Effective Health Care Program

Comparative Effectiveness Review
Number 132

Combination Therapy Versus Intensification of Statin Monotherapy: An Update

Agency for Healthcare Research and Quality
Advancing Excellence in Health Care • www.ahrq.gov

Comparative Effectiveness Review

Number 132

Combination Therapy Versus Intensification of Statin Monotherapy: An Update

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
www.ahrq.gov

Contract No. 290-2012-00007-I

Prepared by:
Johns Hopkins University Evidence-based Practice Center
Baltimore, MD

Investigators:
Anne K. Monroe, M.D., M.S.P.H.
Kimberly A. Gudzune, M.D., M.P.H.
Ritu Sharma, B.Sc.
Yohalakshmi Chelladurai, M.B.B.S., M.P.H.
Padmini D. Ranasinghe, M.D., M.P.H.
Mohammed T. Ansari, M.B.B.S., M.Med.Sc., M.Phil.
Karen A. Robinson, Ph.D.

AHRQ Publication No. 14-EHC013-EF
February 2014

This report is based on research conducted by the Johns Hopkins University Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-2012-00007-I). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

This report may be used, in whole or in part, as the basis for development of clinical practice guidelines and other quality enhancement tools, or as a basis for reimbursement and coverage policies. AHRQ or U.S. Department of Health and Human Services endorsement of such derivative products may not be stated or implied.

This report may periodically be assessed for the urgency to update. If an assessment is done, the resulting surveillance report describing the methodology and findings will be found on the Effective Health Care Program Web site at www.effectivehealthcare.ahrq.gov. Search on the title of the report.

Persons using assistive technology may not be able to fully access information in this report. For assistance contact EffectiveHealthCare@ahrq.hhs.gov.

None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

Suggested citation: Monroe AK, Gudzune KA, Sharma R, Chelladurai Y, Ranasinghe PD, Ansari MT, Robinson KA. Combination Therapy Versus Intensification of Statin Monotherapy: An Update. Comparative Effectiveness Review No. 132. (Prepared by the Johns Hopkins University Evidence-based Practice Center under Contract No. 290-2012-00007-I.) AHRQ Publication No. 14-EHC013-EF. Rockville, MD: Agency for Healthcare Research and Quality; February 2014. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input.

We welcome comments on this systematic review. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

Richard G. Kronick, Ph.D.
Director
Agency for Healthcare Research and Quality

Jean Slutsky, P.A., M.S.P.H.
Director, Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Stephanie Chang, M.D., M.P.H.
Director, EPC Program
Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Elisabeth U. Kato, M.D., M.R.P.
Task Order Officer
Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Acknowledgments

The authors gratefully acknowledge the continuing support of our AHRQ Task Order Officer, Elisabeth U. Kato. We would like to thank Edgar R. Miller for his thoughtful feedback and Sonal Singh for his input regarding the meta-analysis. We also express our gratitude to the following individuals for their contributions to this project: Oluwakemi Fawole, Shauna Linn, and Brian G. Ockerse.

We extend our appreciation to the members of our Technical Expert Panel (listed below), all of whom provided thoughtful advice and input during our process.

Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

The list of Technical Experts who participated in developing this report follows:

Iffat N. Chowdhury, M.D.
U.S. Food and Drug Administration
Silver Spring, MD

John Wilson Epling, Jr., M.D., FAAFP
State University of New York, Upstate Medical University
Syracuse, NY

Antonio M. Gotto, Jr., M.D., D.Phil., FACC
Weill Medical College, Cornell University
New York, NY

James Howard, M.D., MACP
MedStar Washington Hospital Center
Washington, DC

Neil J. Stone, M.D, MACP, FAHA, FACC
Feinberg School of Medicine, Northwestern University
Chicago, IL

Karol E. Watson, M.D., Ph.D., FACC
Geffen School of Medicine
University of California, Los Angeles
Los Angeles, CA

Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report do not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential nonfinancial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

The list of Peer Reviewers follows:

Elliott Marshall Antman, M.D.
Brigham and Women's Hospital, Harvard Medical School
Boston, MA

Courtney Jordan Baechler, M.D., M.S.
Penny George Institute for Health and Healing
Minneapolis, MN

Iffat N. Chowdhury, M.D.
U.S. Food and Drug Administration
Silver Spring, MD

John Wilson Epling, Jr., M.D., FAAFP
State University of New York, Upstate Medical University
Syracuse, NY

Antonio M. Gotto, Jr., M.D., D.Phil., FACC
Weill Medical College, Cornell University
New York, NY

Lewis Kuller, M.D., Dr.P.H.
University of Pittsburgh Graduate School of Public Health
Pittsburgh, PA

Neil J. Stone, M.D, MACP, FAHA, FACC
Feinberg School of Medicine, Northwestern University
Chicago, IL

Combination Therapy Versus Intensification of Statin Monotherapy: An Update

Structured Abstract

Objective. To assess the benefits and harms of combination of statin and other lipid-modifying medication compared to intensification of statin monotherapy. This is an update to a 2009 review.

Data sources. The search for the prior review included MEDLINE® from 1966 to May 2009, Embase® from 1980 to May 2009, and the Cochrane Library to the third quarter of 2008. Additional searches of MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) from May 2008 to July 2013 were conducted for the update.

Review methods. Paired investigators independently screened search results to assess eligibility. Investigators abstracted data sequentially and assessed risk of bias independently. Investigators graded the strength of evidence (SOE) as a group.

Results. All evidence for clinical outcomes (mortality, acute coronary events, and revascularization procedures) were graded as insufficient when comparing lower potency combination therapy with higher potency statin monotherapy. Results of effects on surrogates—low-density lipoprotein (LDL-c) and high-density lipoprotein (HDL-c)— and on serious adverse events are summarized below:

Bile acid sequestrants (BAS): There was moderate SOE from four trials that a low-potency statin combined with a BAS lowered LDL-c up to 14 percent more than mid-potency statin monotherapy.

Ezetimibe: Moderate SOE from 11 trials favors mid-potency statin with ezetimibe for lowering LDL-c, with reduction up to 18 percent more compared to high-potency statin monotherapy among general populations. Low SOE from 11 trials favors mid-potency statin with ezetimibe for raising HDL-c, with increase up to 6 percent more compared to high-potency statin monotherapy.

Fibrates: There is insufficient evidence to compare combination therapy with fibrate and statin to intensification of statin monotherapy regardless of statin potency.

Niacin: There is insufficient evidence to compare combination therapy with niacin and statin to intensification of statin monotherapy on lowering LDL-c, regardless of statin potency. Moderate SOE from three trials found that low-potency statin with niacin raises HDL-c up to 27 percent more than mid-potency statin monotherapy.

Omega-3 fatty acids: No relevant trials were found.

Conclusions. Although many studies looked at intermediate outcomes, few studies addressed the question of which approach produces better clinical outcomes. Combination of statin with ezetimibe or bile acid sequestrant lowered LDL-c better than intensification of statin monotherapy, but evidence for clinical outcomes (mortality, acute coronary events, and revascularization procedures) was insufficient across all potency comparisons for all combination therapy regimens. Additional studies evaluating long-term clinical benefits and

harms are needed to better inform clinical decisionmaking, patient choice, and clinical practice guidelines.

Contents

Tables

Figures

Appendixes

Executive Summary

Background

Cardiovascular disease (CVD) includes conditions such as coronary heart disease, stroke, heart failure, arrhythmia, heart valve disease, congenital heart disease, and hypertension. The American Heart Association has estimated that CVD affects 83.6 million individuals in the United States, contributes to 32.3 percent of deaths, and is a leading cause of disability.[1] Atherosclerosis (hardening of arteries caused by plaque deposition) causes coronary heart disease (CHD), cerebrovascular disease, and peripheral artery disease. The American Heart Association estimates that atherosclerotic CVD affects 15.4 million Americans.[1] CHD, which includes coronary artery disease, myocardial infarction (MI), unstable angina, and heart failure, is a leading cause of death for both men and women in the United States.[2] It is estimated that by 2030, the prevalence of CHD will rise by 16.6 percent and result in more than $106 billion in direct health care costs.[3]

Abnormal lipoprotein metabolism, especially increased concentrations of apo B-100–containing low-density lipoprotein (LDL-c), predisposes individuals to atherosclerosis. Due to the consistent and robust association of higher LDL-c levels with atherosclerotic CVD across experimental and epidemiologic studies,[4,5] therapeutic strategies to decrease risk have focused on LDL-c reduction as a primary goal. In contrast to LDL-c, high-density lipoprotein (HDL-c) has a protective role against atherosclerotic CVD. Epidemiologic studies have demonstrated an inverse association between HDL-c and CVD, where low HDL-c levels are independent predictors of CHD.[6]

Questions remain as to how best to modify lipid levels with the goal of preventing CHD. The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are the most widely prescribed lipid-lowering agents and are often used as monotherapy. However, some patients do not reach their treatment goals on statin monotherapy or are troubled by side effects, prompting interest in combination therapy as a way to improve lipid levels without having to increase statin dosage or as a way to reduce side effects. Statins can be combined with an additional lipid-modifying medication such as a bile acid sequestrant, cholesterol absorption inhibitor, fibric acid, nicotinic acid, or omega-3 fatty acid. There are potential benefits to treating with multiple agents, as the different mechanisms of action of the other lipid-modifying agents may produce benefits unlikely to be achieved with a statin alone. For example, a fibrate or niacin in combination with a statin may increase HDL-c and decrease triglycerides above what is achieved with statin treatment alone.[7] Combination therapy could potentially result in fewer statin-related side effects (e.g., myalgias and elevated liver transaminases), as lower doses of statin could be used. Conversely, a combination of agents could result in an increase in side effects, as patients may experience the side effects common to both drugs.

In 2009, the Agency for Healthcare Research and Quality released an evidence report comparing combinations of these lipid-modifying agents to statin intensification.[8,9] However, the authors found insufficient evidence to determine whether combination therapy held benefit over monotherapy. To provide additional information for clinicians treating patients with moderate or high CHD risk, this update reviews the most recent evidence.

Two contextual factors need to be kept in mind while considering the evidence comparing statin intensification to combination therapy. First, guideline recommendations about intensifying statin therapy or adding an additional nonstatin agent to achieve a specific lipid target level have recently changed.[10] The National Cholesterol Education Program (NCEP) Adult

Treatment Panel (ATP) III provided guidelines on both when to initiate lipid-lowering therapy based on LDL-c level and CHD risk factors and recommended LDL-c targets for optimal CHD risk reduction.[11,12] However, the new guidelines for treatment of cholesterol to reduce atherosclerotic CVD, released in November 2013, represent a major change from the ATP III guidelines. No specific LDL-c targets (e.g., LDL-c ≤70 mg/dL) were presented in the new guidelines due to the lack of evidence from randomized controlled trials supporting specific targets. Rather, four "statin benefit groups" were identified: individuals with clinical atherosclerotic CVD, individuals with LDL-c ≥190 mg/dL, people with diabetes aged 40–75, and individuals aged 40–75 with a ≥7.5-percent 10-year atherosclerotic CVD risk. For individuals within these groups, there are recommendations for treatment with moderate- or high-potency statins. The expected response to a moderate-potency statin is an LDL-c reduction of 30 to 50 percent, while the expected response to a high-potency statin is an LDL-c reduction of ≥50 percent. For individuals who do not have the expected response, adherence is assessed. Then the guidelines recommend considering intensification of statin therapy if the patient is not at maximum dose or the addition of a nonstatin agent with proven efficacy in reducing CVD events.[10]

Second, several large trials, such as ENHANCE (The Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression), AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL Cholesterol/High Triglyceride and Impact on Global Health Outcomes), and ACCORD (Action to Control Cardiovascular Risk in Diabetes)-Lipid, have compared statin monotherapy to combination therapy with the same statin dose plus another lipid-lowering drug. These trials have demonstrated that "add-on" combination therapy can lead to superior lipid outcomes but fails to reduce atherosclerosis or lead to decreased rates of cardiovascular death, MI, revascularization, or stroke.[13] This evidence calls into question previous assumptions that lowering LDL-c or raising HDL-c are always reliable predictors of improved clinical outcomes, as well as increasing the importance of patient-centered clinical outcomes for evaluating the effectiveness of lipid-modifying therapies.[7,14]

Scope and Key Questions

We aimed to assess the effectiveness, safety, and tolerability of the combination of statin and other lipid-modifying medication compared to intensification of statin monotherapy. Our scope was limited to comparing the combination of statin with other lipid-modifying medication to intensification of statin monotherapy. We did not examine the separate but related question of whether adding another lipid-modifying agent to the same potency statin therapy will improve clinical outcomes (add-on combination therapy). Therefore, a number of high-profile studies that evaluated add-on combination therapy, including ACCORD, AIM-HIGH, HSP-2 THRIVE (Heart Protection Study 2 Treatment of HDL to Reduce the Incidence of Vascular Events), and ENHANCE, are not included in this review. We did not expand our update to evaluate add-on combination therapy for two reasons: (1) the upcoming release of the IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International) trial results, which will be critical in characterizing the effect of add-on combination therapy with ezetimibe + statin on clinical outcomes, thereby making a review at this time premature; and (2) resource constraints. Furthermore, we did not include nonstatin monotherapy as a comparison group, given that statins are the first-line treatment for dyslipidemia and the focus of this update is on populations that can tolerate statins at some dose. We aimed to answer the questions below by reviewing trials of adults that compared a higher potency of statin monotherapy to a lower potency statin in combination with another agent (bile acid sequestrant, ezetimibe, fibrate, niacin, or omega-3 fatty acid).

The specific Key Questions (KQs) are:

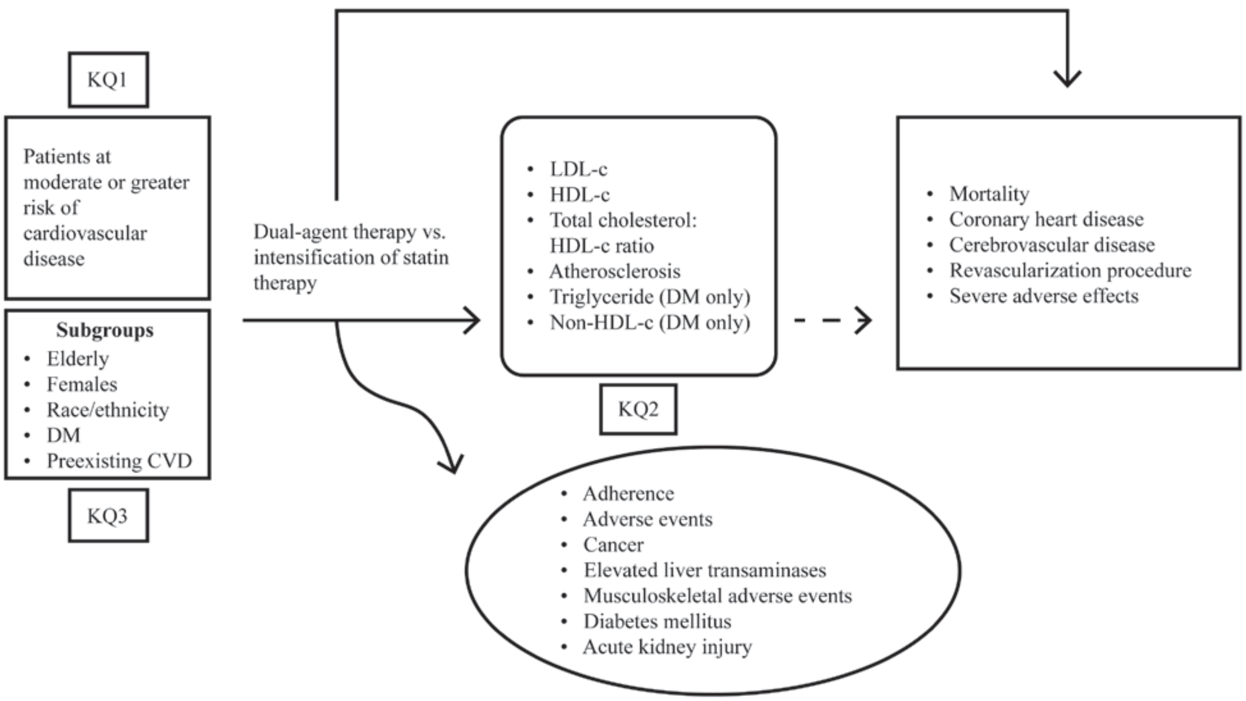
KQ 1: For patients who require intensive lipid-modifying therapy, what are the comparative long-term benefits and rates of serious adverse events of coadministration of different lipid-modifying agents (i.e., a statin plus another lipid-modifying agent) compared with higher dose statin monotherapy?

KQ 2: Do these regimens differ in reaching LDL targets (or other surrogate markers), short-term side effects, tolerability, and/or adherence?

KQ 3: Compared with higher dose statins and with one another, do combination regimens differ in benefits and harms within subgroups of patients?

The analytic framework for our review is shown in Figure A.

Figure A. Analytic framework for comparative effectiveness of lipid-modifying agents



CVD = cardiovascular disease; DM = diabetes mellitus; HDL-c = high-density lipoprotein; KQ = Key Question; LDL-c = low-density lipoprotein

Methods

Search Strategy, Study Selection, and Data Abstraction

We searched the following databases for primary studies: MEDLINE®, Embase®, and the Cochrane Central Register of Controlled Trials (CENTRAL) from May 2008 through July 2013. We also reviewed relevant review articles. In addition, we requested and reviewed Scientific Information Packets provided by the pharmaceutical manufacturers.

Abstract and full-text screening was performed by two independent reviewers using prespecified eligibility criteria (Table A). All articles included in the prior review were reviewed during the full-text screen. Conflicts were resolved by consensus adjudication.

Data abstraction was conducted with a senior reviewer (faculty-level project investigator) abstracting data from articles while having access to the first reviewer's data abstraction. Differences in opinion were resolved through consensus adjudication and, for difficult cases, during team meetings.

Table A. Study inclusion and exclusion criteria

Population and Condition of Interest	Included adults with moderate (10-year CHD risk 10-20% or LDL-c ≥160 mg/dL) or high (10-year CHD risk ≥20% or LDL-c ≥190 mg/dL) cardiovascular disease risk. *Excluded* studies if they included only adults with low cardiovascular disease risk (CHD risk <10% or LDL-c <160 mg/dL). *Excluded* studies that included only patients with homozygous FH.
Interventions and Approaches	Studies must have evaluated a combination regimen of interest. Included studies of bile acid sequestrants + statin. Included studies of ezetimibe + statin. Included studies of fibrates + statin. Included studies of niacin + statin. Included studies of omega-3 fatty acids + statin. *Excluded* studies of lifestyle modifications. *Excluded* studies of drugs approved only for the treatment of homozygous FH. *Excluded* studies of drugs not approved by the FDA or investigational drugs. *Excluded* studies of prepackaged medications that contained non–lipid-lowering medications.
Comparisons of Interest	Included comparisons with higher potency statin monotherapy. *Excluded* studies if a study statin monotherapy was of the same or lower potency than combination arm. *Excluded* studies if there was no comparison or only placebo comparison.
Outcomes and Timing	Included clinical outcomes—mortality, cardiovascular events, cerebrovascular events, and revascularization procedures at any time point. Included surrogate outcomes—LDL-c, HDL-c, TC:HDL-c ratio, NCEP ATP III LDL-c target attainment, and measures of atherosclerosis at any time point. Included triglycerides and non–HDL-c in diabetes subgroup. Included adherence and harms outcomes—adherence, serious adverse events (as reported by investigators), withdrawal due to adverse events, cancer, elevated liver transaminases, adverse +musculoskeletal events, diabetes mellitus, and acute kidney injury at any time point.
Type of Study	Included studies with any sample size that met all other criteria. Included studies from the prior report that met all other criteria.[a] Included randomized controlled trials Included nonrandomized extension of clinical trial over 24 weeks duration (clinical outcomes, SAE, and harms only). Included FDA reports (SAE and harms only). *Excluded* studies with other observational designs. *Excluded* studies with no original data (reviews, editorials, comments, letters, modeling-only studies). *Excluded* studies published only as abstracts. *Excluded* qualitative studies. *Excluded* crossover trials with fewer than 4 weeks washout and/or lacking paired observation, within-person differences, or precrossover data. *Excluded* non–English-language publications.

CHD = coronary heart disease; FDA = U.S. Food and Drug Administration; FH = familial hypercholesterolemia; HDL-c = high-density lipoprotein; LDL-c = low-density lipoprotein; NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel IIL; SAE = serious adverse event; TC = total cholesterol

[a]Sharma M, Ansari MT, Soares-Weiser K, Abou-setta AM, Ooi TC, Sears M, Yazdi F, Tsertsvadze A, Moher D. Comparative Effectiveness of Lipid-Modifying Agents. Comparative Effectiveness Review No. 16. (Prepared by the University of Ottawa Evidence-based Practice Center under Contract No. 290-02-0021.) Rockville, MD: Agency for Healthcare Research and Quality. September 2009. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Risk-of-Bias Assessment

Risk of bias was assessed independently by two reviewers using the Cochrane Collaboration's tool. For studies included from the prior review, we used the quality assessments from that report, which used the Jadad Score.

Data Synthesis

We compared lower potency statins in combination therapy with higher potency statin monotherapy, which enabled us to synthesize data across statin type and statin dose. We used specific criteria to determine statin potency (Table B).

Table B. Different dosing of specific statins based on potency to reduce LDL-c

Potency	Atorvastatin (mg/day)	Fluvastatin (mg/day)	Fluvasatin XL (mg/day)	Lovastatin (mg/day)	Pitavastatin (mg/day)	Pravastatin (mg/day)	Rosuvastatin (mg/day)	Simvastatin (mg/day)
Low potency (<30% LDL-c reduction)	5	20 and/or 40	--	5 and/or 10 and/or 20	1	10 and/or 20 and/or 40	--	10
Mid potency (30-40% LDL-c reduction)	10	80	80	40 and/or 80	2 and/or 4	80	2.5[a]	20
High potency (>40% LDL-c reduction)	20 and/or 40 and/or 80	--	--	--	--	--	5 and/or 10 and/or 20 and/or 40	40 and/or 80[b]

LDL-c = low-density lipoprotein
[a]Dose not included in this review; information obtained from "FDA Advisory Committee Meeting Briefing Document NDA 21-366 for the use of CRESTOR" (www.fda.gov/ohrms/dockets/ac/03/briefing/3968b1_02_a-fda-clinical%20review.pdf).
[b]Studies that used simvastatin 80 mg in statin-naïve patients were excluded.

We calculated and displayed the mean differences with 95-percent confidence intervals for the individual studies grouped by combination therapy agent, statin potency, and population for all comparisons. We considered meta-analysis where there were three or more similar studies. We report qualitative synthesis of data for most outcomes because of the lack of outcomes meeting our criteria for meta-analysis and significant heterogeneity detected when meta-analyses were conducted (I^2 >50%).

Strength of the Body of Evidence

We graded the quantity, quality, and consistency of the evidence for the following outcomes: mortality, acute coronary events, revascularization procedures, serious adverse events, LDL-c, and HDL-c. We used an evidence grading scheme recommended by the "Methods Guide for Effectiveness and Comparative Effectiveness Reviews."[15] We created evidence grades for each comparison and outcome by combination agent, statin potency, and population. We used four domains to yield a final evidence grade: risk of bias, consistency, directness and precision.

The final strength-of-evidence (SOE) grades were: (1) "high" grade (indicating high confidence that the evidence reflects the true effect and further research is very unlikely to change our confidence in the estimate of the effect); (2) "moderate" grade (indicating moderate confidence that the evidence reflects the true effect and further research may change our confidence in the estimate of the effect and may change the estimate); (3) “low” grade (indicating low confidence that the evidence reflects the true effect and further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate); and (4) “insufficient” grade (no evidence identified). A comparison-outcome pair with high SOE was one with low risk of bias, directness, consistency, and precision. Moderate SOE indicated that a high risk of bias was noted or that two of the following were observed: a moderate risk of bias, inconsistency, indirectness, or imprecision. Low SOE indicated a high risk of bias and two or more of the following or a moderate risk of bias and three of the following: inconsistency, indirectness, and imprecision.

Investigators writing each section completed the SOE grading, which was then reviewed by the team.

Applicability

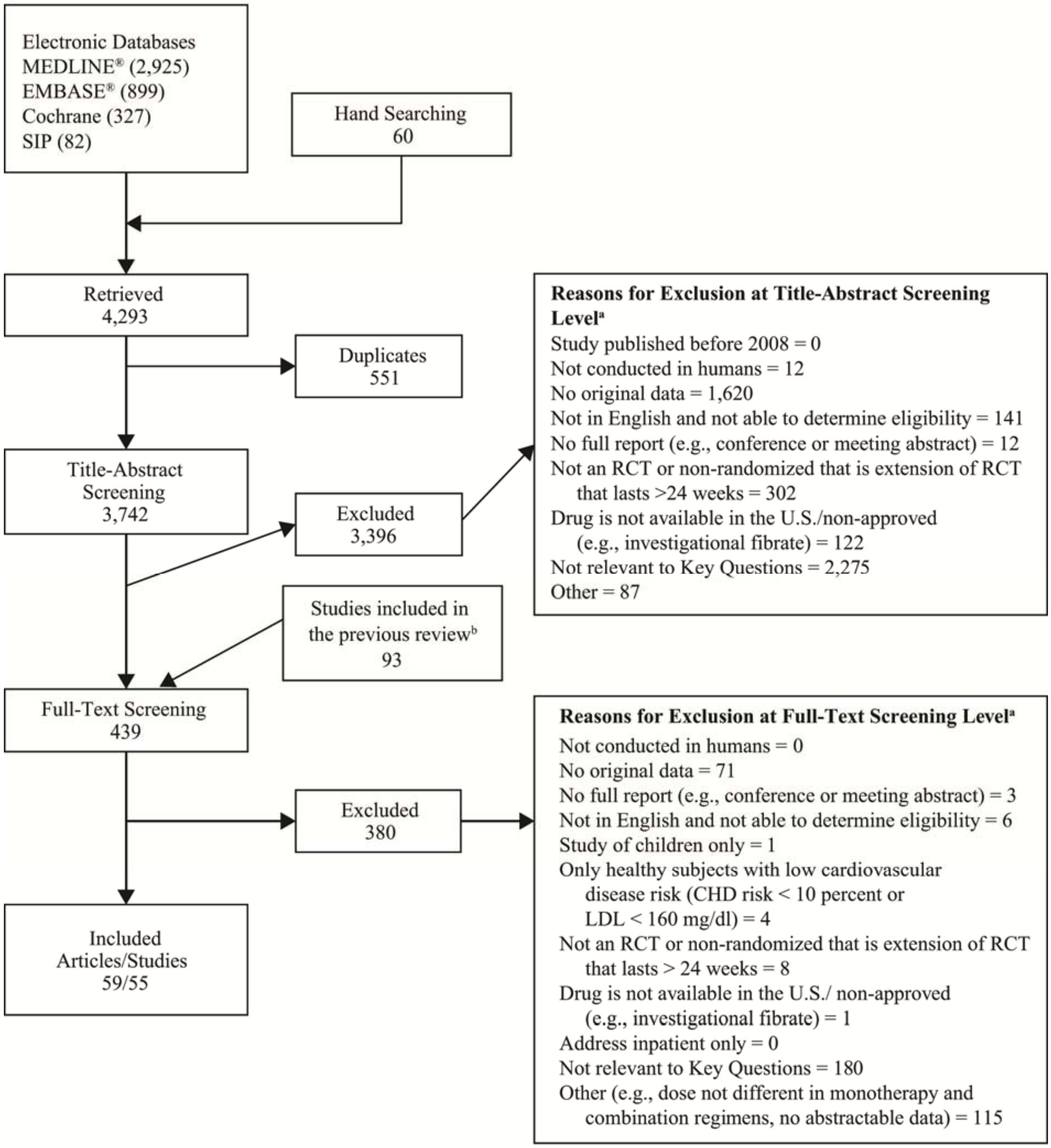
We describe the applicability of studies in terms of the degree to which the study population, interventions, outcomes, and settings were relevant to individuals at high CHD risk requiring aggressive lipid-modifying therapy and features that may affect the effectiveness of the intervention.

Results

Results of Literature Searches

Figure B summarizes the search results. The literature search identified 4,293 unique citations. During the title and abstract screening we excluded 3,396 citations; during the article screening we excluded 380 citations (see Appendix D in the full report). Fifty-five studies, reported in 59 articles, were included. All trials were randomized controlled trials.

Figure B. Summary of search (number of articles)



CHD = coronary heart disease; LDL = low-density lipoprotein; RCT = randomized controlled trial; SIP = Scientific Information Packet

[a]Total exceeds the number of citations in the exclusion box because citations could be excluded for more than one reason.

[b]Sharma M, Ansari MT, Soares-Weiser K, Abou-setta AM, Ooi TC, Sears M, Yazdi F, Tsertsvadze A, Moher D. Comparative Effectiveness of Lipid-Modifying Agents. Comparative Effectiveness Review No. 16. (Prepared by the University of Ottawa Evidence-based Practice Center under Contract No. 290-02-0021.) Rockville, MD: Agency for Healthcare Research and Quality. September 2009. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Overview of Included Trials by Potency and Agent

The SOE was variable across comparisons evaluating the effectiveness and safety of combination therapy versus intensification of statin monotherapy. Evidence for all the clinical outcomes of mortality, acute coronary events, and revascularization procedures was graded as insufficient across all potency comparisons for all combination therapy regimens.

Seven comparisons had moderate SOE for LDL-c and HDL-c outcomes. However, all other comparisons and outcomes had low or insufficient evidence. The interventions and approaches that effectively lowered LDL-c or raised HDL-c are described by combination therapy regimen below. The SOE for the body of evidence is provided in Table C for general populations and Table D for subgroups.

Table C. Summary of the strength of evidence for general populations

Combination Agent	Potency Comparison (Combination Therapy vs. Monotherapy)	Clinical Events			Serious Adverse Events	Surrogate Markers	
		Mortality	Acute Coronary Events	Revascularization Procedures		LDL-c	HDL-c
Bile Acid Sequestrant	Low-potency combination therapy vs. high-potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
	Mid-potency combination therapy vs. high-potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
	Low-potency combination therapy vs. mid-potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	**Moderate: Combination therapy favored, with 0-14% greater LDL-c reduction**	Insufficient
Ezetimibe	Low-potency combination therapy vs. high-potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	**Low: Combination therapy favored, with 2-12% greater LDL-c reduction**	**Low: Combination therapy favored, with up to 5-6% greater increase in HDL-c**
	Mid-potency combination therapy vs. high-potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	**Moderate: Combination therapy favored, with 3-14% greater LDL-c reduction**	**Low: Combination therapy favored, with 2-6% greater increase in HDL-c**
	Low-potency combination therapy vs. mid-potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	**Moderate: Combination therapy favored, with 311% greater LDL-c reduction**	**Low: Combination therapy favored, with 3-4% greater increase in HDL-c**

Table C. Summary of the strength of evidence for general populations (continued)

Combination Agent	Potency Comparison (Combination Therapy vs. Monotherapy)	Clinical Events			Serious Adverse Events	Surrogate Markers	
		Mortality	Acute Coronary Events	Revascularization Procedures		LDL-c	HDL-c
Fibrates	Low-potency combination therapy vs. high-potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
	Mid-potency combination therapy vs. high-potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
	Low-potency combination therapy vs. high-potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Niacin	Low-potency combination therapy vs. high-potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
	Mid-potency combination therapy vs. high-potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
	Low-potency combination therapy vs. mid-potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	**Moderate: Combination therapy favored, with 15-27% greater increase in HDL-c**
Omega-3 Fatty Acid	Low-potency combination therapy vs. high-potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
	Mid-potency combination therapy vs. high-potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
	Low-potency combination therapy vs. mid-potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient

HDL = high-density lipoprotein; LDL-c = low-density lipoprotein

Note: Comparisons for which there was evidence are shown in bold.

Table D. Summary of the strength of evidence for subgroups

Subgroup	Combination Agent	Potency Comparison (Combination Therapy Vs. Monotherapy)	Clinical Events			Serious Adverse Events	Surrogate Markers	
			Mortality	Acute Coronary Events	Revascularization Procedures		LDL-c	HDL-c
Preexisting CHD	Ezetimibe	Low-potency combination therapy vs. high-potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
		Mid-potency combination therapy vs. high-potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	**Moderate: Combination therapy favored, with 5-15% greater LDL-c reduction**	**Low: No between-group difference in raising HDL-c**
		Low-potency combination therapy vs. mid-potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
	Fibrates	Mid-potency combination therapy vs. high-potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Diabetes	Ezetimibe	Low-potency combination therapy vs. high-potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
		Mid-potency combination therapy vs. high-potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	**Moderate: Combination therapy favored, with 3-21% greater LDL-c reduction**	**Moderate: Combination therapy favored, with 2-6% greater increase in HDL-c**
		Low-potency combination therapy vs. mid-potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
	Fibrates	Low-potency combination therapy vs. mid-potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient

CHD = coronary heart disease; HDL-c = high-density lipoprotein; LDL-c = low-density lipoprotein
Note: Comparisons for which there was evidence are shown in bold.

Combination Therapy Versus Intensification of Statin Monotherapy

Combination Therapy With Bile Acid Sequestrant and Statin

Six randomized trials (410 participants) were identified. Four trials compared low-potency statin in combination with a bile acid sequestrant to mid-potency statin monotherapy (288 participants). Low-potency statin in combination with a bile acid sequestrant lowers LDL-c up to 14 percent more than mid-potency statin monotherapy (SOE: moderate). There was insufficient evidence to evaluate LDL-c outcomes for other potency comparisons or to compare HDL-c outcomes at any statin potency.

We found insufficient evidence to compare combined lipid-modifying therapy with a bile acid sequestrant and statin to intensification of statin monotherapy on the rates of serious adverse events, regardless of statin potency. No study reported on the comparative effectiveness of bile acid sequestrant plus statin on benefits or harms as compared to intensification of statin monotherapy among subgroups.

Combination Therapy With Ezetimibe and Statin

Forty randomized trials (10,955 participants) were identified, which primarily reported on surrogate outcomes such as LDL-c and HDL-c. Thirteen trials compared low-potency statin in combination with ezetimibe to high-potency statin monotherapy in general populations. Among general populations, low-potency statin in combination with ezetimibe more effectively lowers LDL-c and raises HDL-c than high-potency statin monotherapy (SOE: low).

Eleven trials compared mid-potency statin in combination with ezetimibe to high-potency statin monotherapy in general populations. Mid-potency statin combined with ezetimibe more effectively lowers LDL-c and raises HDL-c than high-potency statin monotherapy among general populations (SOE: moderate and low, respectively).

Six trials compared low-potency statin in combination with ezetimibe to mid-potency statin monotherapy in general populations. Low-potency statin in combination with ezetimibe more effectively lowers LDL-c and raises HDL-c than mid-potency statin monotherapy (SOE: moderate and low, respectively).

Twelve trials among patients with preexisting CHD and four trials among patients with diabetes compared mid-potency statin in combination with ezetimibe to high-potency statin monotherapy. Mid-potency statin combined with ezetimibe more effectively lowers LDL-c than high-potency statin monotherapy among patients with CHD (SOE: moderate); however, there was no difference in HDL-c effects (SOE: low). Mid-potency statin combined with ezetimibe more effectively lowers LDL-c and raises HDL-c than high-potency statin monotherapy among patients with diabetes (SOE: moderate).

Combination Therapy With Fibrate and Statin

Four randomized trials (1,341 participants) were identified. Two trials compared mid-potency statin in combination with fibrate to high-potency statin monotherapy (683 participants). There is insufficient evidence to compare the benefits of combined lipid-modifying therapy with a fibrate and statin to intensification of statin monotherapy on LDL-c, HDL-c, and serious adverse events, regardless of statin potency.

Combination Therapy With Niacin and Statin

Five randomized trials (612 participants) were identified. Three trials compared low-potency statin in combination with niacin to mid-potency statin monotherapy (247 participants). We found inconsistent effects on lowering LDL-c when comparing low-potency statin in combination with niacin to mid-potency statin monotherapy. However, low-potency statin in combination with niacin raised HDL-c 15 percent to 27 percent more than mid-potency statin monotherapy (SOE: moderate).

We found insufficient evidence to compare combined lipid-modifying therapy with niacin and statin to intensification of statin monotherapy on the rates of long-term clinical outcomes and serious adverse events, regardless of statin potency. No study reported on the effectiveness of niacin plus statin compared to intensification of statin monotherapy on benefits or harms among subgroups.

Combination Therapy With Omega-3 Fatty Acid and Statin

No trials were identified that compared combination therapy with omega-3 fatty acid and statin to intensification of statin monotherapy. There is insufficient evidence to compare the benefits of combined lipid-modifying therapy with an omega-3 fatty acid and statin to intensification of statin monotherapy on LDL-c, HDL-c, and serious adverse events, regardless of statin potency.

Discussion

Key Findings

The evidence suggests that some combination therapy regimens may confer benefits with respect to lowering LDL-c, including bile acid sequestrants (up to 14 percent greater LDL-c reduction) and ezetimibe (up to 21 percent greater LDL-c reduction). LDL-c is an important factor in the development of atherosclerotic cardiovascular disease, and higher levels of LDL-c have been associated with greater risk of this disease.[4,5] However, there is insufficient evidence to address whether the LDL-c–lowering benefits achieved with these medications translate into decreased rates of atherosclerotic cardiovascular disease. Prior trials comparing combination regimens to statin monotherapy, such as ENHANCE, AIM-HIGH, and ACCORD-Lipid, have demonstrated that combination therapy can lead to superior lipid outcomes but fail to reduce clinical outcomes such as cardiovascular death, MI, revascularization, or stroke.[7,13,14]

We also found that some combination therapy regimens may confer benefits with respect to raising HDL-c, including ezetimibe (up to 6 percent) and niacin (up to 27 percent). In particular, given that only one prior study has demonstrated the benefit of pharmacologically raising HDL-c with respect to prevention of CVD events,[16] the potential long-term clinical benefits of these combination regimens with respect to their HDL-c effects are unclear.

The strength of evidence is provided for all observed comparisons in general populations in Table C and for subgroups in Table D. Most trials included in this report were of relatively short duration (<3 months). In this limited timeframe, investigators are unlikely to capture any changes in a chronic condition such as atherosclerotic cardiovascular disease, which typically develops and progresses over a number of years. Powering such studies is especially difficult, given that both arms are taking statins, which would reduce the baseline incidence of cardiovascular events. Therefore, currently it is not possible to draw conclusions about the clinical implications of the surrogate marker changes identified. However, until additional data are available, these results may help health care providers tailor lipid-modifying regimens based on individual patient needs and concerns for adverse events.[17]

Applicability

Many trials that met our inclusion criteria were implemented in patients with hyperlipidemia, and most were designed to evaluate effects on lipid measures and short-term harms. The results of most trials generalize to patients with hyperlipidemia uncomplicated by other major comorbid conditions. Interestingly, we identified fewer trials that were conducted among patients at high risk for CHD, such as those with diabetes or preexisting cardiovascular disease. These patients could benefit the most from improvement in their lipid profiles and are the most likely to be receiving more aggressive lipid-modifying regimens in clinical practice.

Limitations of the Evidence Base and Review Process

The SOE was insufficient for many comparisons and outcomes because of a paucity of studies and poor quality of existing studies. Trials were frequently downgraded in risk-of-bias assessment for lack of blinding by participant and study personnel (performance bias), for not reporting the blinding of outcome assessors (detection bias), or for not accounting for losses to followup or handling of incomplete data (attrition bias). Few studies reported variance estimates for the between-group differences in any outcomes over time. In some instances, the studies did not report a mean difference or point estimate, stating only that there was no significant difference between the groups. In addition, some studies did not report an intention-to-treat analysis and others did not specify the number analyzed in each arm. All of these factors limited our ability to conduct meta-analyses. Where we conducted meta-analyses, substantial heterogeneity was present in most cases.

The evidence base was also limited due to the short duration of most studies. Most trials we identified were of relatively short duration, despite the fact that these medications are currently used in clinical practice as chronic long-term medications. Studies were of insufficient duration to adequately assess long-term clinical outcomes, including mortality, acute coronary events, and revascularization procedures. In addition, losses to followup and medication adherence were often not reported by intervention arm in trials, which may bias our results. While our findings may suggest that one therapeutic option provides a benefit over another, we cannot comment on the tolerability of or persistence with the regimen, given the lack of data and short trial duration. Additional long-term trials are needed to compare the tolerability, side effects, and harms with prolonged use of these combinations.

The review process imposed limitations as well. First, the review focused narrowly on combination therapy compared with statin intensification. As a result, many studies of add-on combination therapy versus the same statin dose or nonstatin monotherapy were excluded because they did not address the Key Questions. Given several previous reviews on dietary modification and reduction of lipids and CVD risk, we did not include these therapies in this review.[18,19] Further, we did not examine differences in statin response based on genetic variations.[20,21] Second, we excluded non–English-language publications, although we do not believe this introduced significant bias. Third, because this review was conducted prior to the release of the 2013 cholesterol treatment guidelines from the American College of Cardiology/American Heart Association Task Force, we could not define our population eligibility criteria to match their four "statin benefit groups" and our potency categorizations differ slightly from those in the guidelines.[10]

Future Research Needs

We suggest that most comparisons and outcomes that have low or insufficient evidence are future research needs. In order to answer whether there are long-term benefits with respect to mortality, acute coronary events, and revascularization procedures, future investigators need to make these endpoints the primary outcomes of their trials and ensure that trials are of sufficient duration to actually capture these events (at least 12 months and preferably longer). Short-term trials using surrogate endpoints are of diminishing value at this point.

We further suggest that future studies focus on high-risk CHD populations and populations with greater burden of cardiovascular disease to determine which strategy provides better short-term improvements in lipid profile and long-term clinical benefits. These populations include patients with diabetes and preexisting cardiovascular disease, as well as Black and Native American populations.[22] It may be worthwhile to explore differences between men and women, as the ACCORD trial showed benefit of combination therapy with fibrate in men and potential harms with this combination therapy in women.[14] Such studies would have tremendous impact on clinical practice, as these patients with greater burden of cardiovascular disease are the most likely to need a more aggressive lipid-modifying regimen.

While head-to-head comparisons of a combination regimen to intensification of statin therapy may answer important clinical questions, these trials do not help clinicians decide between different combination therapy options. Once the effectiveness of each combination regimen on long-term clinical outcomes is established, the next step to inform clinical decisionmaking would be to help clinicians determine how to select the most appropriate lipid-modifying regimen from all available options. We suggest that future studies conduct head-to-head comparisons of multiple combination regimens against each other as well as against intensification of statin monotherapy to address this need. Additionally, it would be useful to examine whether it is possible to achieve LDL-c reductions consistent with those from potent statins (50–60%) in patients who are unable to tolerate full-dose statin therapy and what the clinical effects of these reductions would be. Furthermore, it would be useful to determine if LDL-c lowering of 50 percent achieved with a statin and a bile acid sequestrant is as efficacious as similar LDL-c lowering with a statin and ezetimibe, and whether both used together are as efficacious as a potent statin alone. Finally, alternative study designs, such as observational studies using registry data from electronic medical records, may also provide useful data on clinical outcomes.

Conclusions

Although many studies looked at intermediate outcomes, few studies addressed the question of which approach produces better clinical outcomes. Combination of statin with ezetimibe or bile acid sequestrant lowered LDL-c better than intensification of statin monotherapy, but evidence for clinical outcomes (mortality, acute coronary events, and revascularization procedures) was insufficient across all potency comparisons for all combination therapy regimens. Additional studies evaluating long-term clinical benefits and harms are needed to better inform clinical decisionmaking, patient choice, and clinical practice guidelines.

References

1. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics--2013 update: a report from the American Heart Association. Circulation. 2013;127(1):e6-e245. PMID: 23239837.

2. Mosca L, Barrett-Connor E, Wenger NK. Sex/gender differences in cardiovascular disease prevention: what a difference a decade makes. Circulation. 2011;124(19):2145-54. PMID: 22064958.

3. Heidenreich PA, Trogdon JG, Khavjou OA, et al. Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. Circulation. 2011;123(8):933-44. PMID: 21262990.

4. Pekkanen J, Linn S, Heiss G, et al. Ten-year mortality from cardiovascular disease in relation to cholesterol level among men with and without preexisting cardiovascular disease. N Engl J Med. 1990;322(24):1700-7. PMID: 2342536.

5. Cui Y, Blumenthal RS, Flaws JA, et al. Non-high-density lipoprotein cholesterol level as a predictor of cardiovascular disease mortality. Arch Intern Med. 2001;161(11):1413-9. PMID: 11386890.

6. Barter P, Gotto AM, LaRosa JC, et al. HDL cholesterol, very low levels of LDL cholesterol, and cardiovascular events. N Engl J Med. 2007;357(13):1301-10. PMID: 17898099.

7. Boden WE, Probstfield JL, Anderson T, et al. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. N Engl J Med. 2011;365(24):2255-67. PMID: 22085343.

8. Sharma M, Ansari MT, Abou-Setta AM, et al. Systematic review: comparative effectiveness and harms of combination therapy and monotherapy for dyslipidemia. Ann Intern Med. 2009;151(9):622-30. PMID: 19884623.

9. Sharma M, Ansari MT, Soares-Weiser K, et al. Comparative Effectiveness of Lipid-Modifying Agents [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2009 Sep. Report No. 09-EHC024-EF. AHRQ Comparative Effectiveness Reviews. PMID: 20704039.

10. Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013 Nov 7:S0735-1097(13)06028-2. PMID: 24239923.

11. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation. 2002;106(25):3143-421. PMID: 12485966.

12. Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. J Am Coll Cardiol. 2004;44(3):720-32. PMID: 15358046.

13. Kastelein JJ, Akdim F, Stroes ES, et al. Simvastatin with or without ezetimibe in familial hypercholesterolemia. N Engl J Med. 2008;358(14):1431-43. PMID: 18376000.

14. Ginsberg HN, Elam MB, Lovato LC, et al. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med. 2010;362(17):1563-74. PMID: 20228404.

15. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(11)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality; March 2011. Chapters available at www.effectivehealthcare.ahrq.gov.

16. Robins SJ, Collins D, Wittes JT, et al. Relation of gemfibrozil treatment and lipid levels with major coronary events: VA-HIT: a randomized controlled trial. JAMA. 2001;285(12):1585-91. PMID: 11268266.

18. Rees K, Dyakova M, Ward K, et al. Dietary advice for reducing cardiovascular risk. Cochrane Database Syst Rev. 2013;(3):CD002137. PMID: 23543514.

19. Hooper L, Summerbell CD, Thompson R, et al. Reduced or modified dietary fat for preventing cardiovascular disease. Cochrane Database Syst Rev. 2012;(5):CD002137. PMID: 22592684.

20. SEARCH Collaborative Group, Link E, Parish S, et al. SLCO1B1 variants and statin-induced myopathy--a genomewide study. N Engl J Med. 2008; 359(8):789-99. PMID: 18650507.

21. Krauss RM, Mangravite LM, Smith JD, et al. Variation in the 3-hydroxyl-3-methylglutaryl coenzyme a reductase gene is associated with racial differences in low-density lipoprotein cholesterol response to simvastatin treatment. Circulation. 2008;117(12):1537-44.

22. Liao Y, Bang D, Cosgrove S, et al. Surveillance of health status in minority communities - Racial and Ethnic Approaches to Community Health Across the U.S. (REACH U.S.) Risk Factor Survey, United States, 2009. MMWR Surveill Summ. 2011; 60(6):1-44. PMID: 21597458.

Introduction

Cardiovascular Disease (CVD)

Cardiovascular disease (CVD) includes conditions such as coronary heart disease, stroke, heart failure, arrhythmia, heart valve disease, congenital heart disease, and hypertension. The American Heart Association (AHA) has estimated that CVD affects 83.6 million individuals, contributes to 32.3 percent of deaths, and CVD is a leading cause of disability.[1] CVD prevalence has been projected to rise in the future, with over 40 percent of the U.S. population having CVD by 2030.[2] In addition, the total direct medical costs attributable to CVD are expected to increase from $273 billion in 2010 to $818 billion by 2030.[3]

While CVD is the leading cause of death for men and women, some gender differences exist. The CVD death rate for U.S. women is estimated as 123.7 per 100,000 women, while for U.S. men the estimated CVD death rate is 249.8 per 100,000 men.[1] In addition, there are differences in rates of CVD by race/ethnicity. Recently, the Centers for Disease Control examined differences in self-reported CVD by race/ethnicity. They found that Native American and black men self-reported higher proportions of CVD (13.4% and 9.4%, respectively) as compared to the median percentage of men with CVD among the locations surveyed (8.8%), while Hispanic and Asian men had lower percentages (7.7% and 6.6%, respectively).[4] A similar trend was seen for women; the median percentage of women with CVD was 6.3 percent, while 12.4 percent of Native American women, 10.3 percent of black women, 5.7 percent of Hispanic women, and 4.4 percent of Asian women reported having CVD.[4]

Atherosclerotic CVD and Lipids

Atherosclerosis plays a major role in the development of atherosclerotic CVD, which is a subset of CVD that includes coronary heart disease (CHD), cerebrovascular disease, and peripheral artery disease. The American Heart Association estimates that atherosclerotic CVD affects 15.4 million Americans.[1] CHD, which includes coronary artery disease (CAD), myocardial infarction (MI), unstable angina (UA), and heart failure, is a leading cause of death for both men and women in the U.S.[5] By 2030, the prevalence of CHD will rise by 16.6 percent and result in over $106 billion in direct healthcare costs.[3]

Role of LDL in Atherosclerotic CVD

Abnormal lipoprotein metabolism predisposes individuals to atherosclerosis, especially increased concentrations of apo B-100-containing low-density lipoprotein (LDL-c). Oxidized LDL-c is atherogenic, causing endothelial damage, alteration of vascular tone, and recruitment of monocytes and macrophages.[6] Many studies have underscored the importance of LDL-c in development of atherosclerotic CVD.[7,8] Due to the consistent and robust association of higher LDL-c levels with atherosclerotic CVD across experimental and epidemiologic studies, therapeutic strategies to decrease risk have focused on LDL-c reduction as a primary goal. While the prevalence of elevated LDL-c levels among adults has decreased by 33 percent from 1999 to 2006, the most recent estimates still report that 28 percent of U.S. adults have elevated LDL-c.[1]

Role of Other Lipoproteins in Atherosclerotic CVD

In contrast to LDL-c, high-density lipoprotein (HDL-c) has been associated with reduced risk of atherosclerotic CVD. HDL-c may inhibit LDL-c oxidation through various enzymes, as well as reverse cholesterol transport.[6] These enzymes stop the formation of or destroy the atherogenic, oxidized LDL-c, thereby preventing the inflammatory reaction that results in endothelial damage and plaque formation. Epidemiologic studies have demonstrated an inverse association between HDL-c and CVD. Low HDL-c levels are independent predictors of CHD[9,10] and have been associated with increased CVD risk among patients without vascular disease at baseline.[11] However, only the VA-HIT study showed clinical benefit of raising HDL-c among men with low baseline HDL-c.[12]

Evidence for Lipid-Modifying Therapy

Lipid-modifying medications include 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, bile acid sequestrants, cholesterol absorption inhibitor, fibric acids, nicotinic acid, and omega-3 fatty acids, which have various mechanisms of action and pharmacokinetic properties. Table 1 provides an overview of the expected lipid effects of these agents based on mechanism of action and reported effects in clinical trials.

Table 1. Lipid modifying agents and their expected lipid effects

Agent	LDL	HDL
HMG-CoA Reductase Inhibitors	Decrease	Increase
Bile Acid Sequestrants[a]	Decrease	None
Cholesterol Absorption Inhibitor	Decrease	None
Fibric Acids	Variable	Increase
Nicotinic Acid	Decrease	Increase
Omega-3 Fatty Acids	Variable	None

[a]Contraindicated in patients with triglycerides more than 300 mg/dl.

Mechanism of Action of HMG-CoA Reductase Inhibitors

The most widely prescribed lipid-lowering agents are the HMG-CoA reductase inhibitors or “statins.” These agents inhibit the enzyme, HMG-CoA reductase, which is the catalyst for the rate-limiting step in cholesterol synthesis throughout the body.[13] As a result, the lower intracellular cholesterol concentration triggers increased expression of hepatic LDL receptors, which then enhances the clearance of LDL-c from the plasma.[14] Statins may also inhibit hepatic synthesis of apolipoprotein B-100, as well as decrease the synthesis and secretion of other lipoproteins.[15,16] Studies have demonstrated that statins result in significant reductions in LDL-c, and modest increases in HDL-c.[17,18]A recent meta-analysis of trials targeting LDL-c reduction with statins found that reducing LDL-c by 39 mg/dL resulted in reductions in the annual incidence of MI, revascularization, and ischemic stroke by one fifth.[19] The effect size for improvement in these outcomes increases after the third year of therapy (RR of major vascular event per 1 mmol/L reduction in LDL–C 0.72 at Year 3)[19] Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials.[19] Statins may also contribute to regression of atherosclerosis,[20] stabilize plaque,[21] decrease inflammation,[22] and reduce endothelial dysfunction.[23] Statins have shown clear benefits in overall mortality and in primary and secondary prevention of CHD. In patients without CHD, statins have decreased nonfatal myocardial infarctions,[24] incidence of a first major coronary event,[25,26] and all-cause mortality.[27] In patients with known CHD or CHD risk equivalents (e.g., diabetes), statins reduce major coronary events, cardiovascular mortality, and all-cause mortality.[28,29] Another meta-analysis found that statin use reduced all-cause mortality by 17 percent, reduced fatal and non-fatal CVD endpoints by 30 percent, and reduced the revascularization rates by 34 percent.[30] There are 7 statins currently approved by the FDA: atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin. There have been concerns regarding adverse effects of intensive statin therapy. For example, intensive statin therapy has been associated with an increased risk of diabetes compared to moderate statin therapy.[31] Rhabdomyolysis is a rare but dangerous complication of statin with higher risk at higher statin doses.[32,33]

Mechanism of Action of Bile Acid Sequestrants

Bile acid sequestrants (BAS) bind bile acids in the bowel, which prevents them from being reabsorbed the intestine and effectively interrupts their enterohepatic circulation.[34] As a result, the liver increases its synthesis of cholesterol and uptake of circulating LDL-c to produce more of these bile acids. This process ultimately results in the lowering of circulating LDL-c. BAS have no effects on HDL. There are 3 BAS currently approved by the FDA: cholestyramine, colesevelam, and colestipol.

Mechanism of Action of Cholesterol Absorption Inhibitor

Cholesterol absorption inhibitor blocks the Niemann-Pick C1-like protein (NPC1L1) in the small intestine, which thereby prevents the uptake of cholesterol from the gut. Ultimately, this process leads to relative depletion of cholesterol in the liver, which responds by increasing cholesterol synthesis and uptake of circulating LDL-c.[35,36] This process ultimately results in the lowering of circulating LDL-c. Cholesterol absorption inhibitor has no effects on HDL-c.[37,38] Currently, there is one FDA approved cholesterol absorption inhibitor, ezetimibe.

Mechanism of Action of Fibric Acids

Fibric acids or “fibrates” may modulate lipoprotein levels through a variety of mechanisms including induction of lipoprotein lipolysis, induction of fatty acid uptake, reduction of hepatic triglyceride production, increased removal of LDL-c particles, and increased production of HDL-c.[39] Typically, fibrates will result in a mild decrease in LDL-c, mild increase in HDL-c, and significantly reduce triglycerides. There are 3 fibrates currently approved by the FDA: fenofibrate, fenofibric acid, and gemfibrozil.

Mechanism of Action of Nicotinic Acid

Nicotinic acid or “niacin” inhibits the synthesis of LDL-c, as well as delays clearance of circulating HDL-c.[40] Typically, niacin moderately decreases LDL-c and moderately increases HDL-c.[41,42] Niacin has demonstrated modest benefit in decreasing nonfatal recurrent MI, but has not lead to decreases in mortality.[43] Niacin is the only nicotinic acid currently approved by the FDA, and comes in three forms: immediate/regular release (Niacor®): sustained/controlled release (over-the-counter formulations) and extended release (Niaspan®). Adverse effects such as flushing may vary with these forms.

Mechanism of Action of Omega-3 Fatty Acids

Dietary consumption of marine-sourced omega-3 fatty acids has been linked with positive cardiovascular benefits for many years. Available prescription omega-3 fatty acids contain eicosapentaenoic acid (EPA) with/without docosahexaenoic acid (DHA). While the mechanism of omega-3 fatty acids is not fully understood, they have been hypothesized to inhibit acyl CoA:1,2 diacylglycerol acyltransferase, increase hepatic beta-oxidation, reduce the hepatic synthesis of triglycerides, or increase plasma lipoprotein lipase activity. Typically, omega-3 fatty acids lead to decreases in triglycerides and potentially increase large particle LDL-c, which may be less atherogenic.[44] These medications were linked with reduced risk of death, nonfatal MI and nonfatal stroke in early research;[45] however, more recent studies have not shown a reduction in CVD outcomes with omega-3 fatty acid therapy.[46] There are currently 2 omega-3 fatty acids approved by the FDA: omega-3 acid ethyl ester and icosapent ethyl.

Current Guidelines and Controversies for Lipid-Modifying Therapy

Until recently, lipid therapy focused on attaining different presepcified cholesterol targets based upon pateints CVD risk. The National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III provided guidelines on both when to initiate lipid-lowering therapy based on LDL-c level and CHD risk factors and recommended LDL-c targets for optimal CHD risk reduction.[2] Clinicians could use statin monotherapy or combination therapy with statin and another agent to achieve these LDL-c goals. There are potential benefits to treating with multiple agents, as the different mechanisms of action of the other lipid-modifying agents may produce other benefits unlikely to be achieved with statin alone. For example, a fibrate or niacin in combination with a statin may increase HDL-c and decrease triglycerides above what is achieved with statin treatment alone.[47] Conversely, a combination of agents could result in an increase in side effects, as patients may experience the side effects common to both drugs. Individual agents may have benefits on non-lipid outcomces in particular groups. For example, colesevelam HCl, one of the bile acid sequestrants, has been shown to lower HbA1c when used in diabetic patients on oral agents or insulin.[48]

Despite the generally favorable effects of combination regimens on surrogate lipid markers in clinical trials, combination regimens have not consistently been shown to improve clinical outcomes.[47,47,49,50] In the ACCORD trial, the addition of fenofibrate to simvastatin did not reduce the rates of cardiovascular deaths, MI or stroke more than same-dose simvastatin monotherapy among patients with diabetes.[51] In addition, this combination therapy conferred possible benefit for men and possible harms for women. In the AIM-HIGH trial, patients with preexisting atherosclerotic CVD received niacin in addition to simvastatin or simvastatin monotherapy.[47] While the patients taking combination therapy had greater increases in their HDL-c, there were no benefits on incidence of cardiovascular death, MI, stroke, or revascularization procedures. The ENHANCE compared the effect of ezetimibe in addition simvastatin to simvastatin alone on carotid intima-media thickness (CIMT) in patients with hyperlipidemia. There was no difference in CIMT changes between the two groups despite significantly lower LDL-c levels in the combination therapy group. However, the subsequent ARBITER-6 HALTS study comparing statin+niacin with statin+ezetimibe revealed lower incidence of major cardiovascular events with statin+niacin than with statin+ezetimibe.[50] Interestingly, the CVD benefits with combination therapy with niacin seen in ARBITER-6 HALTS was not replicated in AIM-HIGH, as the trial showed no reduction in CVD outcomes from adding niacin to a statin.[47] Based on the combination of findings from these trials, investigators have suggested that ezetimibe either has no effect on or possibly worsens CVD outcomes as a possible theory to explain these discrepancies.[50] The ongoing IMPROVE-IT trial will compare ezetimibe added to simvastatin to simvastatin monotherapy on cardiovascular death, MI, revascularization, or stroke (completion expected in September 2014) may help clarify the picture.[52] Overall, these trials comparing statin monotherapy to combination therapy with the same statin dose plus another lipid lowering drug have demonstrated that this "add on" combination therapy can lead to superior lipid outcomes, but fails to reduce atherosclerosis or lead to decreased rates of cardiovascular death, MI, revascularization, or stroke.[53]

These studies call into question previous assumptions that lowering LDL-c or raising HDL-c are always reliable predictors of improved clinical outcomes. The ACCF, AHA, American College of Physicians, and others have advocated for the approach of prescribing at least a moderate dose statin to all patients with ischemic coronary heart disease, regardless of LDL-c value.[54] New ACC/AHA lipid management guidelines released in November 2013 reflect this approach. No specific LDL-c targets (e.g. LDL-c ≤ 70 mg/dL) were presented in the new guidelines given the lack of RCT evidence supporting specific targets. Rather, four "statin benefit groups" were identified: individuals with clinical atherosclerotic CVD, individuals with LDL-c ≥ 190 mg/dL, diabetics aged 40-75, and individuals aged 40-75 with a ≥ 7.5% 10-year atherosclerotic CVD risk. Individuals in one of these groups are recommended for treatment with moderate- or high-potency statin monotherapy. The expected response to a moderate-potency statin is an LDL-c reduction of 30-50%, while the expected response to a high-potency statin is an LDL-c reduction of ≥ 50%. For individuals who do not have an expected response, once adherence has been assessed, the guidelines recommend considering intensification of statin therapy if the patient is not at maximum dose or the addition of a non-statin agent with proven efficacy in reducing CVD events. In addition, combination therapy can be considered in patients who cannot tolerate a high or moderate potency statin. These guidelines represent a significant change from the ATP III, which has generated considerable discussion around the calculation of CVD risk, lack of cholesterol treatment targets, and reliance on RCT data only.

2013 Update of the Comparative Effectiveness Review: Overview

In 2009, the Agency for Healthcare Research and Quality (AHRQ) released an evidence report examining lipid-modifying agents.[55,56] This prior review initially intended to examine the long-term benefits and rates of serious adverse effects of co-administration of different lipid-lowering agents vs. higher dose statin monotherapy for patients at high CHD risk (ten-year risk > 20%). However, the authors found a paucity of evidence to address this question, so conducted additional analyses unrestricted by patient risk, statin type or statin dose. Despite this increase in scope, the authors concluded that there was insufficient evidence to determine whether combination therapy held benefit over monotherapy. Since the initial review, additional trials on efficacy and safety outcomes have been published. The evidence base for all three key questions has been expanded, which led to the decision to update the prior review.

To provide additional guidance to clinicians treating patients with moderate or high CHD risk, this update review addresses long-term benefits and rates of serious adverse events (SAEs) associated with co-administration of different lipid-modifying agents compared with higher potency statin monotherapy. We included studies examining patients at moderate and high CHD risk, defined as a 10-year CHD risk greater than 10 percent or LDL-c greater than 160 mg/dL, as these patients may require intensive lipid modifying therapy to achieve their LDL-c goals. Studies focusing on lower risk patients with a 10-year CHD risk less than 10 percent were excluded, as these patients are likely to achieve their LDL-c goal with typical statin monotherapy. This update review additionally examines surrogate markers of CHD events including lipid levels and atherosclerosis, as well as side effects/tolerability and medication adherence. Similar to the prior review, we sought to evaluate clinical/surrogate benefits and harms among the following subgroups: females, patients older than 75, diabetics, patients with established vascular disease, and participants of African and Asian descent as well as Hispanics. The choice of subgroups reflects populations in whom the risk of adverse effects, CVD risk, and need for intensive lipid-lowering therapy differs as compared with the general population.

Scope and Key Questions

We aimed to assess the effectiveness, safety, and tolerability of combination of statin and other lipid-modifying medication to intensification of statin monotherapy. Our scope was limited to comparing combination of statin with other lipid-modifying medication to intensification of statin monotherapy as proposed in the key questions. This review will address the important question of whether there is benefit to adding another lipid-modifying agent to lower potency statin compared with higher potency statin monotherapy, which may be particularly relevant for patients who cannot tolerate high-dose statin therapy, yet desire to achieve their LDL-c goals.

Of note, the review does not address other clinical questions. For example, another important question is whether adding on another lipid-modifying agent to the same potency statin therapy will improve clinical outcomes ("add-on" combination therapy). Many of the high-profile studies including ACCORD, AIM-HIGH, HSP-2 THRIVE, and ENHANCE have evaluated add-on combination therapy, and are not included in this review. Another reason for not expanding the scope to evaluate add-on combination therapy was the upcoming release of the results from the IMPROVE-IT trial that will be critical in characterizing the effect of add-on combination therapy with ezetimibe+statin on important clinical outcomes. Several trials have shown that non-statin monotherapy may not improve clinical outcomes; however, we did not include non-statin monotherapy as a comparison group because it was outside the scope of this update. We sought to answer the questions below by reviewing trials of adults that compared a higher potency of statin monotherapy to a lower potency statin in combination with another agent (bile acid sequestrant, ezetimibe, fibrate, niacin, or omega-3 fatty acid).

The analytic framework for the review is shown in Figure 1.

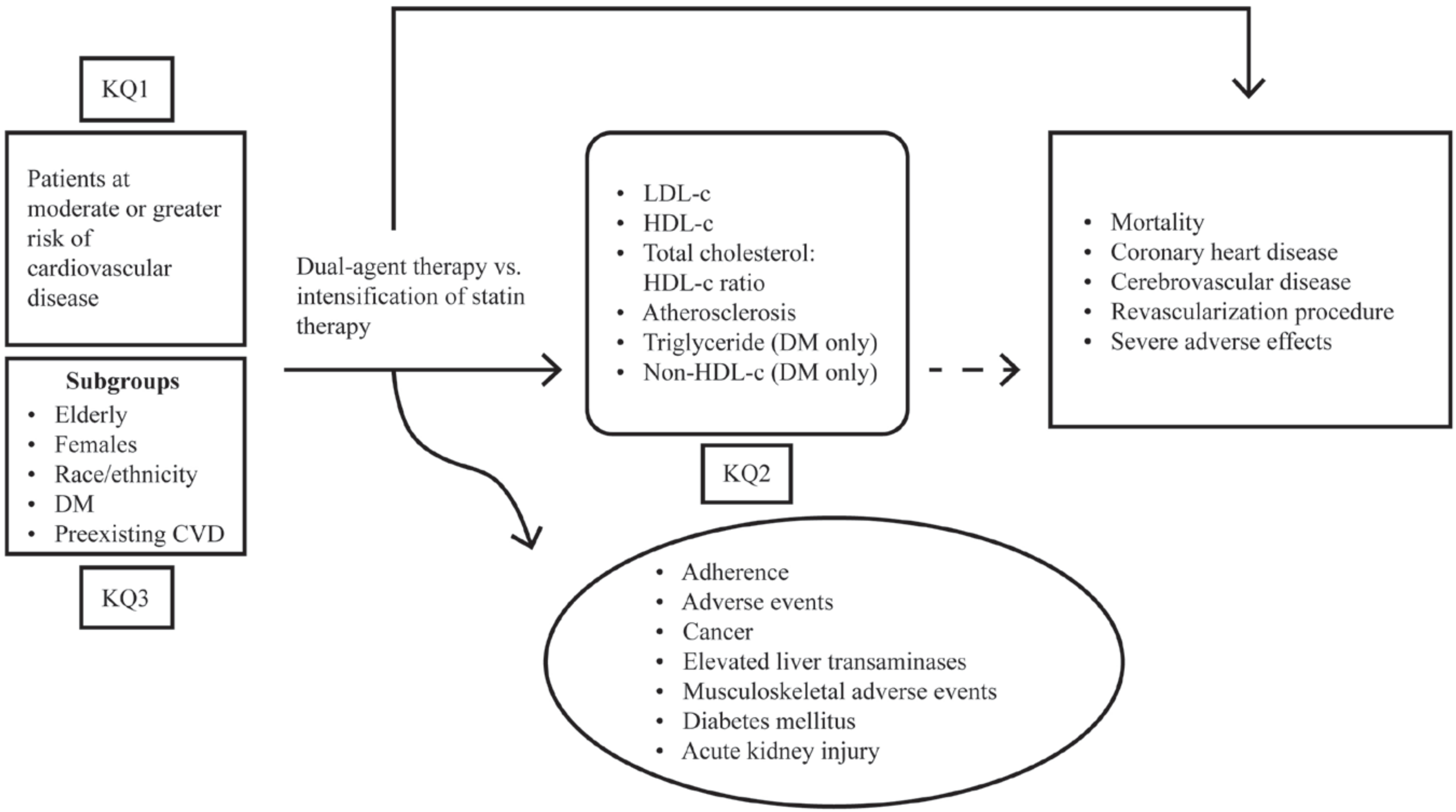
The specific Key Questions (KQ) are:

KQ 1: For patients who require intensive lipid-modifying therapy, what are the comparative long-term benefits and rates of serious adverse events of co-administration of different lipid-modifying agents (i.e., a statin plus another lipid-modifying agent) compared with higher dose statin monotherapy?

KQ 2: Do these regimens differ in reaching LDL targets (or other surrogate markers), short-term side effects, tolerability, and/or adherence?

KQ 3: Compared with higher dose statins and to one another, do combination regimens differ in benefits and harms within subgroups of patients?

Figure 1. Analytic framework for comparative effectiveness of lipid-modifying agents



CVD = cardiovascular disease; DM = diabetes mellitus; HDL = high-density lipoprotein; KQ = Key Question; LDL = low-density lipoprotein

Methods

Topic Development

This review is an update of an evidence report completed in 2009.[56] The summary of changes from the previous systematic review is shown in Table 2. The protocol for our review was posted on the AHRQ Web site (www.effectivehealthcare.ahrq.gov) on May 17, 2013.

Table 2. Summary of changes from prior report

Population	We included adults at moderate and high risk of cardiovascular disease (the prior report had no restrictions by patient CVD risk level). We specifically excluded studies of patients with homozygous familial hypercholesterolemia.
Intervention	We included drugs that were not FDA-approved at the time of the prior review.
Outcomes	We added diabetes mellitus and acute kidney injury/chronic kidney disease as potential harms.
Type of Study and Timing	We reviewed nonrandomized studies that were extensions of RCTs. The prior evidence report considered any nonrandomized study over 24 weeks' duration.
Data Synthesis	In order to avoid multiple comparisons across numerous permutations of lower versus higher dose statins, we grouped statins based on their potency to reduce LDL-c.

Search Strategy

Using the same basic search rules used for the original report (with the addition of terms for newly added drugs), we searched the following databases for primary studies: MEDLINE®, Embase®, and the Cochrane Central Register of Controlled Trials (CENTRAL). Our search strategy for MEDLINE is shown in Appendix B. The search for the prior review included MEDLINE from 1966 to May 2009, Embase from 1980 to May 2009, and The Cochrane Library to the third quarter of 2008. We included an overlap in search dates, per AHRQ guidance on updating reviews,[57] searching MEDLINE from May 2008 to July 2013, Embase from May 2008 to July 2013, and The Cochrane Library from the fourth quarter of 2007 to July 2013. We also reviewed references from relevant review articles. Pharmaceutical companies who produce the drugs included in this review were asked to provide information as Scientific Information Packets (SIPs) about pertinent studies (published or unpublished).

Study Selection

Abstracts were screened independently by two trained reviewers, and were excluded if both reviewers agreed that the article met one or more of the exclusion criteria (see inclusion and exclusion criteria listed in Table 3 and the Abstract Screen Form in Appendix C). In brief, we included randomized controlled trials (RCT) of adults that compared a higher potency of statin monotherapy to a lower potency statin in combination with another agent (bile acid sequestrant, ezetimibe, fibrate, niacin, or omega-3 fatty acid). The clinical outcomes of interest were mortality, coronary heart disease events, cerebrovascular events, revascularization procedures, and serious adverse events (as reported by investigators), while our surrogate clinical outcomes included lipid measures (e.g., LDL-c, HDL-c), atherosclerosis, and medication adherence. Triglycerides and non-HDL-c were only considered for diabetic subgroup as per ATP III guidelines. Adverse effects included cancer, elevated liver transaminases, musculoskeletal adverse events, diabetes mellitus, and acute kidney injury. Given the limited duration of many RCTs, we also considered observational trials to examine clinical outcomes, serious adverse events and harms. As in the prior evidence report, we considered non-randomized comparative studies of 24 weeks or more in duration for clinical outcomes, serious adverse events, and harms, which were extensions of controlled clinical trials. These are trials in which patients are unblinded and continue to receive the therapies they were originally assigned. Finally, we also searched FDA reports for serious adverse events and harms. Differences between reviewers regarding abstract eligibility were resolved through consensus.

Citations promoted on the basis of abstract screen underwent independent paired-reviewer screen using the full text article (Appendix C, Article Screen Form). Differences regarding article inclusion were resolved through consensus.

At this level, we also screened all studies included in the prior review to ensure that they met the current eligibility criteria.

Table 3. List of inclusion/exclusion criteria

Population and condition of interest	Adults with moderate (10-year CHD risk 10-20% or LDL≥160 mg/dL) or high (10-year CHD risk≥20% or LDL≥190 mg/dL) cardiovascular disease risk *Excluded* studies if they included only adults with low cardiovascular disease risk (CHD risk<10% or LDL<160 mg/dL) *Excluded* studies that included only patients with homozygous familial hypercholesterolemia (FH)
Interventions and approaches	Studies must have evaluated a combination regimen of interest Included studies of bile acid sequestrants + statin Included studies of ezetimibe + statin Included studies of fibrates + statin Included studies of niacin + statin Included studies of omega-3 fatty acids + statin *Excluded* studies of lifestyle modifications *Excluded* studies of drugs approved only for the treatment of homozygous FH *Excluded* studies of drugs not approved by the FDA or investigational drug *Excluded* studies of prepackaged medications that contained non lipid-lowering medications
Comparisons of interest	Included comparisons of higher potency statin monotherapy *Excluded* studies if a study statin monotherapy was of the same or lower potency than combination arm *Excluded* studies if there was no comparison, only placebo comparison, or comparison to other combination therapy regimen.
Outcomes and Timing	Clinical outcomes including mortality, cardiovascular events, cerebrovascular events, revascularization procedures at any time point Surrogate outcomes including LDL-c, HDL-c, TC:HDL-c ratio, NCEP ATP IIL LDL-c target attainment, measures of atherosclerosis (e.g., carotid intimal media wall thickness, coronary artery calcification score, etc) at any time point. Triglycerides and non-HDL-c in diabetes subgroup. Adherence and harms outcomes including adherence, serious adverse events (as reported by investigators), withdrawal due to adverse events, cancer, elevated liver transaminases, adverse musculoskeletal events, diabetes mellitus, acute kidney injury at any time point

Table 3. List of inclusion/exclusion criteria (continued)

Type of study	Included studies with any sample size that met all other criteria. Included studies from the prior report that met all other criteria. Included randomized controlled trials () Included non-randomized extension of clinical trial over 24 weeks duration (clinical outcomes, SAE and harms only), and Included FDA reports (SAE and harms only) *Excluded* studies with other observational designs. *Excluded* studies with no original data (reviews, editorials, comments, letters, modeling only studies). *Excluded* studies published only as abstracts. *Excluded* qualitative studies. *Excluded* crossover trials with fewer than 4 weeks washout and/or lacking paired observation, within person differences, or pre-crossover data. *Excluded* non-English publications.

CHD = coronary heart disease; FDA = Food and Drug Administration; FH = familial hypercholesterolemia; HDL = high-density lipoprotein; LDL = low-density lipoprotein; RCT = randomized controlled trial; SAE = serious adverse event; TC = total cholesterol

Data Abstraction and Data Management

We used DistillerSR (EvidencePartners, 2010) to manage the screening process. We uploaded to the system all citations identified by the search strategies.

We created and pilot tested standardized forms for data extraction (Appendix C). We used the Systematic Review Data Repository™ (SRDR) for data abstraction. Data were exported from SRDR into a project-specific database (Access, Microsoft, Redmond, WA) to serve as archived copy and to create evidence tables and summary tables.

Reviewers extracted information on general study characteristics (e.g., study design, study period, and followup), study participants (e.g., age, sex, race/ethnicity, etc.), eligibility criteria, interventions (e.g., medication name, medication dose), outcome measures and the method of ascertainment, and the results of each outcome including measures of variability. We incorporated cross-over trials by taking all measurements from combination regimen intervention periods and all measurements from monotherapy regimen intervention periods and analyzing them as if the trial were a parallel group trial. One reviewer completed data abstraction and a second reviewer confirmed the first reviewer's abstraction for completeness and accuracy. Because data previously abstracted from the trials included in the prior review were incomplete for our needs, we abstracted the data from the studies that met the current eligibility criteria in order to have a complete repository of data for analysis. Reviewer pairs included personnel with both clinical and methodological expertise. We resolved differences between reviewer pairs through discussion and, as needed, through consensus among the larger group of investigators.

Risk of Bias Assessment

We used the Cochrane Collaboration's tool for assessing the risk of bias of controlled studies.[58] Two trained reviewers independently assessed the included studies according to the guidelines in Chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions. For studies included from the prior review, we used the prior quality assessments reported, which were based on the Jadad Score.

Data Synthesis

For each KQ, we created a detailed set of evidence tables containing all information abstracted from eligible studies. We integrated the results of all studies (RCTs + NRSs) qualitatively. In all comparisons, we noted that the evidence base uses different statins both within studies (monotherapy arms uses one statin and combination therapy uses a different statin) and across studies. In addition, a variety of statin doses were also used across studies. Therefore, synthesizing data by statin and statin dose would limit the number of studies amenable to pooling. A recent systematic review grouped statins and statin doses based on their potency to reduce LDL-c (Table 4).[59] We opted to use this potency strategy to group together different statins and statin doses to make comparisons, which increased out number of studies amenable to pooling. This represents a change from the approach used in the original review, in which statins were grouped according to dose.

Table 4. List of different dosing of specific statins based on potency to reduce LDL-c

Statin	Atorvastatin (mg/day)	Fluvastatin (mg/day)	Fluvasatin XL (mg/day)	Lovastatin (mg/day)	Pitavastatin (mg/day)	Pravastatin (mg/day)	Rosuvastatin (mg/day)	Simvastatin (mg/day)
Low Potency (<30% LDL reduction)	5	20 and/or 40	--	5 and/or 10 and/or 20	1	10 and/or 20 and/or 40	--	10
Mid Potency (30-40% LDL reduction)	10	80	80	40 and/or 80	2 and/or 4	80	2.5[a]	20
High Potency (>40% LDL reduction)	20 and/or 40 and/or 80	--	--	--	--	--	5, 10, 20 and/or 40	40 and/or 80[b]

[a]Dose not included in this review; information obtained from "FDA Advisory Committee Meeting Briefing Document NDA 21-366 for the use of CRESTOR."
[b]Studies that use simvastatin 80mg in statin naïve patients will be excluded.

Meta-analysis was considered for outcomes selected as most important for grading the strength of evidence (see below). Studies were grouped such that meta-analyses included the same potency comparisons (i.e., high potency monotherapy versus mid potency combination therapy). For studies that had two monotherapy arms of the same potency, we used only one of these arms as the comparator to the combination arm(s). We used the following rules to select which monotherapy arm to use:

1. If the arms use the same statin, we used the arm with the higher dose.
2. If the arms use different statins, we selected the arm based on the following prioritization of statin agent if it met higher potency criteria: rosuvastatin, atorvastatin, simvastatin, lovastatin, pravastatin, fluvastatin.[60] We identified no studies that used pitavastatin.

We only conducted meta-analyses when there were sufficient data (at least 3 studies of the same design that reported or provided data to calculate SE for difference in differences) and studies were judged to be sufficiently homogenous with respect to key variables (population characteristics, intervention, and outcome). Many studies did not provide sufficient data to calculate SE for difference in differences. When SE was available for most studies included within a specific comparison, we imputed the SE for these other studies. We averaged the reported SE and used this value for the imputed SE.[61] We then conducted sensitivity analysis by completing meta-analyses with and without the imputed SE.

For studies amenable to meta-analysis, we calculated a weighted mean difference using a random effects model with the DerSimonian and Laird formula for continuous outcomes.[62] We evaluated statistical heterogeneity among studies using an I^2 statistic. We had no dichotomous or event outcomes that met our criteria to consider conducting meta-analyses. Given the lack of outcomes meeting our criteria for meta-analysis and significant heterogeneity detected when meta-analyses were conducted (I^2>50%), we report qualitative synthesis of data for all outcomes. We examined the forest plots to identify trials that appeared to have quite different results and considered if these trials had different characteristics. We plannted to conduct sensitivity analysis by excluding such trials and rerunning meta-analyses, but in all cases we identified no trials meeting this criteria or removing these trials would have left fewer than 3 trials to be pooled. The limited number of studies included in each meta-analysis precluded any further sensitivity analyses of subgroups or meta-regression to determine the source of heterogeneity. All analyses were conducted using STATA versions 11.0 and 12.0 (StataCorp LP).

Strength of the Body of Evidence

We graded the strength of evidence using the grading scheme recommended by the Methods Guide for Effectiveness and Comparative Effectiveness Reviews (Methods Guide).[63] For this report, we graded the strength of evidence for the outcomes determined to be most important: mortality, acute coronary events, revascularization procedures, serious adverse events, LDL-c and HDL-c.

In assigning evidence grades, we considered the four required domains including risk of bias, directness, consistency and precision. For outcomes where meta-analysis was not conducted, precision was determined based on the measures of dispersion provided by the studies. The body of evidence for a particular outcome was also considered imprecise if the results were inconsistent or sample size across trials was considered insufficient. If judgement could not be made on those factors, optimal information size (OIS) was calculated to determine sufficiency of sample size.

We classified the strength of evidence into four basic categories: 1) “high” grade (indicating high confidence that the evidence reflects the true effect, and further research is very unlikely to change our confidence in the estimate of the effect); 2) “moderate” grade (indicating moderate confidence that the evidence reflects the true effect, and further research may change our confidence in the estimate of the effect and may change the estimate); 3) “low” grade (indicating low confidence that the evidence reflects the true effect, and further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate); and 4) “insufficient” grade (evidence is unavailable or does not permit a conclusion). A comparison-outcome pair with high strength of evidence was one with low risk of bias, directness, consistency, and precision. Moderate strength of evidence indicated a high risk of bias was noted or that *two* of the following were observed: a moderate risk of bias, inconsistency, indirectness or imprecision. Low strength of evidence indicated *two* or more of the following: a moderate risk of bias, a high risk of bias, inconsistency, indirectness and imprecision. Our judgments were first based on the ability to make a conclusion (if not able to make a conclusion, then “insufficient” was assigned) and then on the confidence in the conclusion (classified as low, moderate or high with increasing certainty). We considered any study that calculated LDL-c as indirect, as the option to measure LDL-c directly does exist and new evidence exists that the Friedewald equation tends to underestimate LDL-c among high-risk patients.[64]

Investigators writing each section completed the strength of evidence grading. The team members reviewed and discussed grading throughout the report writing.

Applicability

Applicability was assessed separately for the different outcomes for the entire body of evidence guided by the PICOS framework as recommended in the Methods Guide.[65] We considered important population characteristics (e.g., women, minorities, diabetics), treatment characteristics (e.g., statin type, statin potency, length of intervention/therapy, dose escalation), and timing that may cause heterogeneity of treatment effects and limit applicability of the findings.

Peer Review and Public Comment

A full draft report was reviewed by experts and posted for public commentary from August 5, 2013, through September 3, 2013. Comments received from either invited reviewers or through the public comment website were compiled and addressed. A disposition of comments will be posted on the Effective Healthcare Program Web site 3 months after the release of the evidence report.

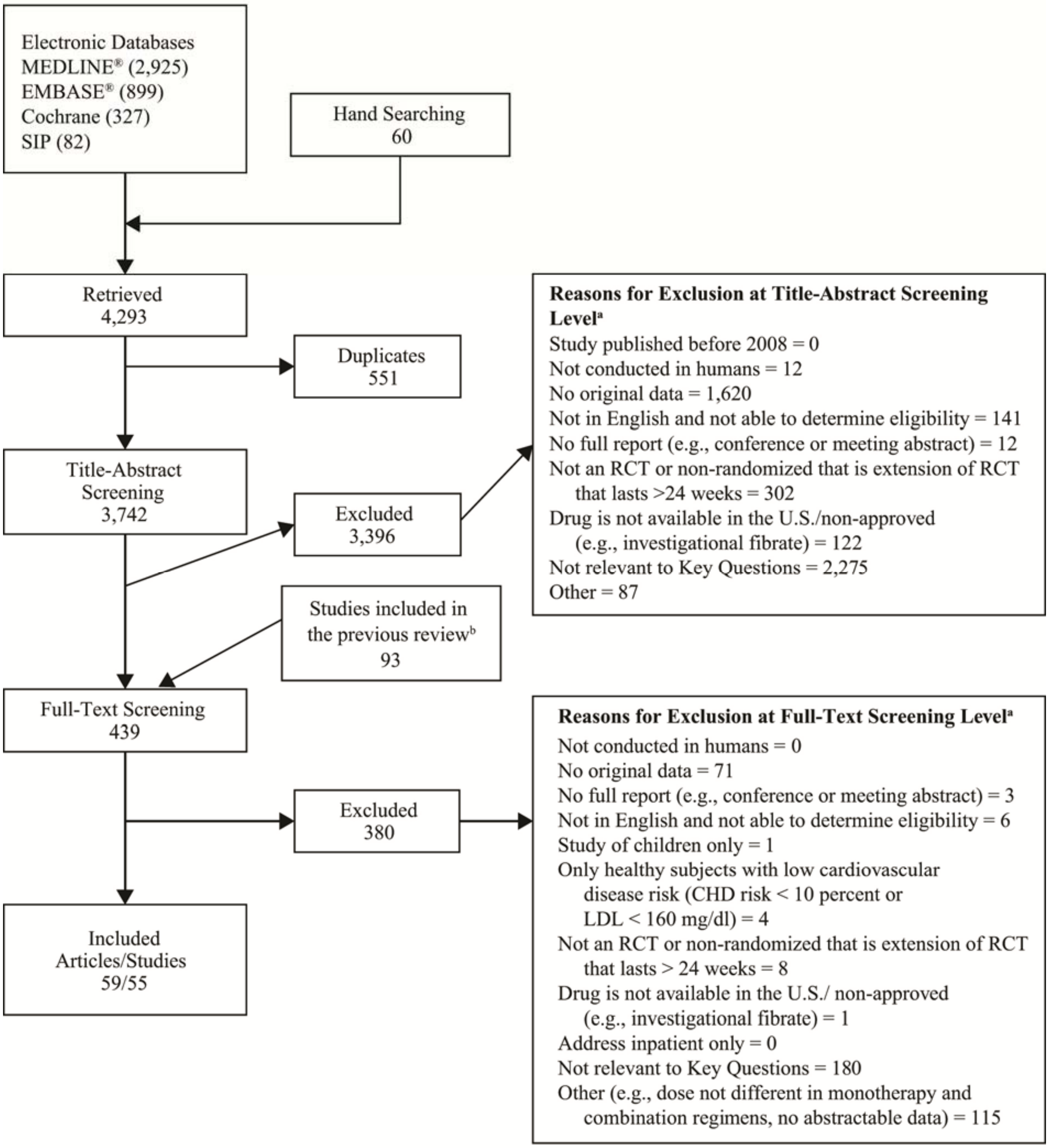
Results

Results of Literature Searches

Figure 2 summarizes the search results. The literature search identified 4,293 unique citations. During the title and abstract screening we excluded 3,396 citations; during the full-text article screening we excluded 380 citations (Appendix D). Of the 14 companies contacted for SIPs, 5 companies responded. One company indicated that no relevant studies had been conducted. Four companies provided SIPs and the references provided by these four companies were carefully crosschecked against our existing database, yielding four new references, none of which were applicable to this review (Appendix E).

Fifty-five studies, all randomized controlled trials, reported in 59 articles, were included.

Figure 2. Summary of search (number of articles)



CHD = coronary heart disease; LDL = low-density lipoprotein; RCT = randomized controlled trial; SIP = Scientific Information Packet

[a]Total exceeds the number of citations in the exclusion box because citations could be excluded for more than one reason.

[b]Sharma M, Ansari MT, Soares-Weiser K, Abou-setta AM, Ooi TC, Sears M, Yazdi F, Tsertsvadze A, Moher D. Comparative Effectiveness of Lipid-Modifying Agents. Comparative Effectiveness Review No. 16. (Prepared by the University of Ottawa Evidence-based Practice Center under Contract No. 290-02-0021.) Rockville, MD: Agency for Healthcare Research and Quality. September 2009. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Overview of Included Trials by Potency and Agent

Of the included trials, 6 trials addressed combination therapy with bile acid sequestrant, 40 trials addressed combination therapy with ezetimibe, 4 trials addressed combination therapy with fibrates, 5 trials addressed combination therapy with niacin and statin, and no trials addressed comparing combination therapy with omega-3 fatty acid (note that one study addressed multiple two combinations: omega 3 and fibrates). Thirty one trials were included from the previous review that met the current eligibility criteria and 28 trials were identified in the new searches (Tables 5 and 6).

Table 5. Randomized trials included in evidence synthesis according to statin potency

Statin	Evidence Report Year	Bile Acid Sequestrants	Ezetimibe	Fibrates	Niacin	Omega-3 Fatty Acids
Low potency combination therapy vs high potency monotherapy	2009	NR	Ballantyne, 2005[66] Bays, 2004[67] Davidson, 2002[68] Goldberg, 2004[69]	Athyros, 2001[70]	NR	NR
	2013	NR	Ahmed, 2008[71] Araujo, 2010[72] Floretin, 2011[73] Lee, 2011[74] Lee, 2012[75] Liberopoulos, 2013[76] Moutzouri, 2011[77] Moutzouri, 2012[78] Rudofsky, 2012[79] Her, 2010[80]	NR	Airan-Javia, 2009 [81]	NR
Mid potency combination therapy vs high potency monotherapy	2009	Hunninghake, 2001[82] Johansson, 1995[83]	Ballantyne, 2003[84] Ballantyne, 2005[66] Barrios, 2005[85] Bays, 2004[67] Catapano, 2006[86] Constance, 2007[87] Davidson, 2002[68] Gaudiani, 2005[88] Goldberg, 2004[69] Goldberg, 2006[89] McKenney, 2007[90] Piorkowski, 2007[91] Roeters van Lennep, 2008[92] Stein, 2004[93]	Athyros, 2001[70] Shah, 2007[94]	Bays, 2003[95]	NR

Table 5. Randomized trials included in evidence synthesis according to statin potency (continued)

Statin	Evidence Report Year	Bile Acid Sequestrants	Ezetimibe	Fibrates	Niacin	Omega-3 Fatty Acids
Mid potency combination therapy vs high potency monotherapy (continued)	2013	NR	Yamazaki, 2013[96] Bardini, 2010[97] Ben-Yehuda, 2011[98]; Zieve, 2010[99]Cho, 2011[100] Foody, 2010[101] Okada, 2011[102] Ostad, 2009[103] Pesaro, 2012[104] Robinson, 2009[105] Tomassini, 2009[106] Hamdan,2011[107] Averna, 2010[108] Lee, 2013[109]	Mohiuddin, 2009[110] Shah, 2007[111]	NR	NR
Low potency combination therapy vs mid potency monotherapy	2009	Barbi, 1992[112] Ismail, 1990[113] PMSG II, 1993[114] Knapp, 2001[115] Schrott, 1995[116]	Ballantyne, 2005[66] Bays, 2004[67] Davidson, 2002[68] Feldman, 2004[117] Goldberg, 2004[69] Kerzner, 2003[118]	NR	Gardner, 1996 [119] Hunninghake, 2003[120] Insull, 2004[121]	NR
	2013	NR	Averna, 2010[108] Hamdan, 2011[107] Kawagoe, 2011[122]	Farnier, 2011[123]	NR	NR

NR = not reported; PMSG II = Pravastatin Multicenter Study Group II

Table 6. Randomized controlled trials included in evidence synthesis according to statin agent

Statin	Evidence Report Year	Bile Acid Sequestrants	Ezetimibe	Fibrates	Niacin	Omega-3 Fatty Acids
Atorvastatin	2009	Hunninghake, 2001[82]	Ballantyne, 2003[84] Piorkowski, 2007[91] Stein, 2004[93]	NR	NR	NR
	2013	NR	Ben-Yehuda, 2011[98] Hamdan, 2011[107] Lee, 2011[74] Lee, 2012[75] Ostad, 2009[103] Zieve, 2010[99]	NR	NR	NR
Fluvastatin	2009	NR	NR	NR	NR	NR
	2013	NR	Kawagoe, 2011[122]	NR	NR	NR
Lovastatin	2009	Schrott, 1995[116]	Kerzner, 2003[118]	NR	Gardner, 1996 [119] Hunninghake, 2003[120] Insull, 2004[121]	NR
	2013	NR	NR	NR	NR	NR
Pitavastatin	2009	NR	NR	NR	NR	NR
	2013	NR	NR	NR	NR	NR
Pravastatin	2009	Barbi, 1992[112] Ismail, 1990[113] PMSG II, 1993[114]	NR	NR	NR	NR
	2013	NR	NR	NR	NR	NR
Rosuvastatin	2009	NR	NR	NR	NR	NR
	2013	NR	Yamazaki, 2013[96]	NR	NR	NR
Simvastatin	2009	Johansson, 1995[83] Knapp, 2001[115]	Bays, 2004[67] Davidson, 2002[68] Feldman, 2004[117] Gaudiani, 2005[88] Goldberg, 2004[69]	NR	NR	NR
	2013	NR	Araujo, 2010[72] Averna, 2010[108] Bardini, 2010[97] Floretin, 2011[73] Liberopoulos, 2013[76] Moutzouri, 2012[78] Pesaro, 2012[104] Rudofsky, 2012[79]	Mohiuddin, 2009[110]	Airan-Javia, 2009 [81]	NR

Table 6. Randomized controlled trials included in evidence synthesis according to statin agent (continued)

Statin	Evidence Report Year	Bile Acid Sequestrants	Ezetimibe	Fibrates	Niacin	Omega-3 Fatty Acids
Mixed Statins	2009	NR	Ballantyne, 2005[66] Barrios, 2005[85] Catapano, 2006[86] Constance, 2007[87] Goldberg, 2006[89] McKenney, 2007[90] Roeters van Lennep, 2008[92]	Athyros, 2001[70] Shah, 2007[94]	Bays, 2003[95]	NR
	2013	NR	Ahmed, 2008[71] Cho, 2011[100] Foody, 2010[101] Moutzouri, 2011[77] Okada, 2011[102] Robinson, 2009[105] Tomassini, 2009[106]	Farnier, 2011[123] Shah, 2007[111]	NR	NR

NR = not reported; PMSG = II Pravastatin Multicenter Study Group II

We present our results by combination agent. Each section follows the format listed below:

1. Study Characteristics
2. Population Characteristics
3. Interventions
4. Outcomes
    - A. Key Points
    - B. Long-term benefits and serious adverse events (KQ1)
        - i. Mortality
        - ii. Acute Coronary Events
        - iii. Cerebrovascular Disease
        - iv. Revascularization Procedures
        - v. Serious Adverse Events
    - C. Surrogate outcomes, short-term side effects and adherence (KQ2)
        - i. LDL
        - ii. HDL
        - iii. Total Cholesterol:HDL
        - iv. Atherosclerosis
        - v. Adherence
        - vi. Any Adverse Event
        - vii. Withdrawal due to Adverse Events
        - viii. Cancer
        - ix. Elevated Liver Transaminases
        - x. Musculoskeletal Adverse Events
        - xi. New Onset Diabetes Mellitus
        - xii. Acute Kidney Injury
    - D. Subgroups of patients (KQ3)
        - i. Patients with pre-existing CHD
            - a. Long-term beneftis and serious adverse events
            - b. Surrogate outcomes, short-term side effects, and adherence
        - ii. Patients with diabetes mellitus
            - a. Long-term beneftis and serious adverse events
            - b. Surrogate outcomes, short-term side effects, and adherence
        - iii. Other subgroups
            - a. Long-term beneftis and serious adverse events
            - b. Surrogate outcomes, short-term side effects, and adherence

Results by Combination Therapy Regimen

Combined Lipid-Modifying Therapy With Statin and Bile Acid Sequestrant Versus Intensification of Statin Monotherapy

Study Characteristics

We included 6 trials (410 participants in eligible arms) that compared bile acid sequestrant plus statin to intensification of statin monotherapy. The 6 trial results were reported in 7 articles.[82,83,112-116] All trials were parallel arm randomized controlled trials. One trial took place in Europe,[83] and all others took place in North America. All trials were multicenter, except for one single center trial.[112,113] Eligibility criteria were similar across all trials. All trials included a dietary run in, followed by treatment ranging from 4 weeks to 24 weeks in duration. Two trials compared high potency statin monotherapy to mid potency statin in combination therapy.[82,83] The other four trials compared mid potency statin monotherapy to low potency statin in combination therapy.[112-116]

Population Characteristics

The average participant was in their 50s with the mean age across trials ranging from 51-61 years. The number of female participants varied between trials. Race was reported in only two trials, where the majority of participants were white.[114,115] Smoking status, prior cardiovascular disease, revascularization events, and diabetes were not consistently reported across trials. When reported, no significant between group differences existed in the trials.[83,114-116]

Interventions

Two trials compared high potency statin monotherapy to mid potency statin in combination with colsevelam[82] or colestipol.[83] These monotherapy arms used atorvastatin and simvastatin, and the combination arms used atorvastatin and simvastatin. Four trials compared mid potency statin monotherapy to low potency statin in combination with cholestyramine[112-114], colsevelam[115], or colestipol.[116] These trials used lovastatin, pravastatin and simvastatin in the monotherapy arms, and lovastatin, pravastatin and simvastatin in the combination therapy arms.

Outcomes

Key Points

- Long-Term Benefits
    - Insufficient evidence for all potency comparisons.
- Serious Adverse Events
    - Insufficient evidence for all potency comparisons.
- Surrogate Outcomes
    - A low potency statin combined with bile acid sequestrant is more effective than mid potency statin monotherapy for lowering LDL-c (SOE: moderate). There is insufficient evidence for other potency comparisons.
    - There is insufficient evidence to evaluate the effectiveness on raising HDL-c for any potency comparison.

- Short-Term Side Effects
    - There is insufficient evidence to compare the rates of elevated liver transaminases for any potency comparison.
    - There is insufficient evidence to compare the rates of elevated creatinine phosphokinase for any potency comparison.
- Adherence
    - Insufficient evidence for all potency comparisons.
- Subgroups
    - Insufficient evidence for all potency comparisons.

Long-Term Benefits and Serious Adverse Events (KQ 1)

No study reported on the comparative effectiveness of bile acid sequestrant plus statin on long-term benefits or rates of serious adverse events as compared to intensification of statin monotherapy among adults. We graded the strength of evidence for mortality, acute coronary events, revascularization procedures, and serious adverse events as insufficient.

Surrogate Outcomes, Short-Term Side Effects and Adherence (KQ 2)

All included RCTs evaluated surrogate outcomes including LDL-c and HDL-c. In several RCTs, medication adherence and short-term side effects were evaluated including elevated liver transaminases and withdrawal due to adverse events. We identified no studies that compared high potency statin monotherapy to low potency statin combination therapy. We identified no eligible non-randomized extensions of RCTs or FDA reports.

LDL-c

Mid Potency Statin Combination Therapy Versus High Potency Statin Monotherapy

Two trials reported on mean percent LDL-c change.[82,83] At 4 weeks, one trial found that statin monotherapy lowered LDL-c 7 percent more than combination therapy.[82] At 12 weeks, the other trial showed that combination therapy with colestipol 10g + simvastatin 20mg lowered LDL-c 5 percent more than statin monotherapy. However, the other combination arm in this trial, which used a lower dose of colestipol (5g) in combination with simvastatin 20mg, was less effective than statin monotherapy at reducing LDL-c (between group difference 2 percent that favored monotherapy). Overall, the results showed inconsistent effects on lowering LDL-c, we graded the strength of evidence as insufficient (Table 7).

Low Potency Statin Combination Therapy Versus Mid Potency Statin Monotherapy

Four trials reported mean percent change in LDL-c (5 comparisons).[112-116] In four comparisons, the difference between combination therapy and statin monotherapy on lowering LDL-c ranged from 8 percent to 14 percent, favoring combination therapy. Duration of therapy ranged from 6 to 12 weeks. One trial that used a lower dose of colestipol with statin in one of its combination arms found no difference between combination therapy and statin monotherapy at lowering LDL-c, which may have contributed to the lack of significant difference in this comparison.[116]

The results of almost all comparisons favored low potency statin in combination with bile acid sequestrant for lowering LDL-c. We graded the strength of evidence as moderate (Table 8).

Only two trials reported or provided sufficient information for us to calculate SE for the LDL-c difference in differences, and therefore, we did not perform meta-analyses.

HDL-c

Mid Potency Statin Combination Therapy Versus High Potency Statin Monotherapy

Two trials reported on mean percent change in HDL-c.[82,83] At 4 weeks, one trial found that combination therapy raised HDL-c 6 percent more than monotherapy.[82] At 12 weeks, the other trial showed that combination therapy with colestipol 5g + simvastatin 20mg raised HDL-c 3 percent more than statin monotherapy. However, the other combination arm in this trial, which used a higher dose of colestipol (10g) in combination with simvastatin 20mg, was less effective than statin monotherapy at raising HDL-c (between group difference 1 percent that favored monotherapy). Overall, the results showed inconsistent effects on raising HDL-c, we graded the strength of evidence as insufficient (Table 7).

Low Potency Statin Combination Therapy Versus Mid Potency Statin Monotherapy

Four trials reported on mean percent change in HDL-c. In these trials,[112-116] the effects on raising HDL-c were inconsistent and showed little to no absolute difference between combination therapy and statin monotherapy (range 2 percent difference in favor of monotherapy to 5 percent difference in favor of combination therapy). Duration of therapy ranged from 6-12 weeks. We graded the strength of evidence as insufficient (Table 8). Only two trials reported or provided sufficient information for us to calculate SE for the LDL-c difference in differences, and therefore, we did not perform meta-analyses.

Total Cholesterol: HDL

No studies reported on total cholesterol:HDL ratio.

Atherosclerosis

No studies reported on atherosclerosis.

Adherence

Mid Potency Statin Combination Therapy Versus High Potency Statin Monotherapy

One trial reported on treatment adherence,[82] which was assessed with a pill count at 4 weeks. In the statin monotherapy arm, adherence was 88 percent and was 91 percent in the combination arm.

Low Potency Statin Combination Therapy Versus Mid Potency Statin Monotherapy

One trial reported on treatment adherence.[116] Adherence to medications was 95 percent in the statin monotherapy arm and 93 percent in the combination arm at 12 weeks. The authors did not describe how adherence with medication was assessed.

Any Adverse Event

No studies reported on the occurrence of any adverse events.

Withdrawal Due to Adverse Events

Mid Potency Statin Combination Therapy Versus High Potency Statin Monotherapy

One trial reported on withdrawals due to adverse events.[82] Both the statin monotherapy arm and the combination therapy arm had one person withdraw.

Low Potency Statin Combination Therapy Versus Mid Potency Statin Monotherapy

Only one trial reported the number of participants who withdrew from the study due to an adverse event.[115] At 6 weeks, no participants in the monotherapy arm had withdrawn, while 1 participant in the combination arm withdrew due to an adverse event.

Cancer

No studies reported on cancer.

Elevated Liver Transaminases

Mid Potency Statin Combination Therapy Versus High Potency Statin Monotherapy

One trial reported on withdrawals due to elevated liver transaminases.[82] No significant elevations of AST and/or ALT >3 times the upper limit of normal occurred in either arm.

Low Potency Statin Combination Therapy Versus Mid Potency Statin Monotherapy

No studies reported elevated liver transaminases.

Adverse Musculoskeletal Events

No studies reported on adverse musculoskeletal events such as elevated CPK, myalgia or rhabodomyolysis.

New Onset Diabetes Mellitus

No studies reported on any diabetes-related outcomes.

Subgroups of Patients (KQ 3)

No study reported on the comparative effectiveness of bile acid sequestrant plus statin on benefits or harms as compared to intensification of statin monotherapy among subgroups.

Table 7. Mid potency statin combination therapy with bile acid sequestrants as compared to high potency statin monotherapy: strength of evidence

Outcome	No. Studies (N)	Risk of Bias	Directness	Consistency	Precision	Reporting Bias Other issues	Findings and Magnitude of Effect	Strength of Evidence
Long-Term Benefits and Serious Adverse Events								
Mortality	None	NA	NA	NA	NA	NA NA	No eligible studies	Insufficient
Acute Coronary Events	None	NA	NA	NA	NA	NA NA	No eligible studies	Insufficient
Revascularization Procedures	None	NA	NA	NA	NA	NA NA	No eligible studies	Insufficient
Serious Adverse Events	None	NA	NA	NA	NA	NA NA	No eligible studies	Insufficient
Surrogate Clinical Outcomes								
LDL-c	2 (122)	Medium [1 trial with Jadad score<3]	Indirect [Calculated LDL in both trials]	Inconsistent [2 comparisons effect favors monotherapy, 1 comparison favors combination therapy]	Imprecise	Not detected None	Two studies with inconsistent results on LDL-c.	Insufficient
HDL-c	2 (122)	Medium [1 trial with Jadad score<3]	Direct [Measured HDL-c in both trials]	Inconsistent [2 comparisons effect favors combination therapy, 1 comparison favors monotherapy]	Imprecise	Not detected None	Two studies with inconsistent results on HDL-c.	Insufficient

HDL = high-density lipoprotein; LDL = low-density lipoprotein; NA = not applicable

Table 8. Low potency statin combination therapy with bile acid sequestrants as compared to mid potency statin monotherapy: strength of evidence

Outcome	No. Studies (N)	Risk of Bias	Directness	Consistency	Precision	Reporting Bias Other Issues	Findings and Magnitude of Effect	Strength of Evidence
Long-Term Benefits and Serious Adverse Events								
Mortality	None	NA	NA	NA	NA	NA NA	No eligible studies	Insufficient
Acute Coronary Events	None	NA	NA	NA	NA	NA NA	No eligible studies	Insufficient
Revascularization Procedures	None	NA	NA	NA	NA	NA NA	No eligible studies	Insufficient
Serious Adverse Events	None	NA	NA	NA	NA	NA NA	No eligible studies	Insufficient
Surrogate Clinical Outcomes								
LDL-c	4 (288)	Medium [2 trials with Jadad score<3]	Indirect [Calculated LDL in all trials]	Consistent [4 comparisons favor combination therapy, 1 comparison no difference]	Imprecise	Not detected None	Studies favor low potency statin in combination with bile acid sequestrant by lowering LDL-c up to 14% more than mid potency statin monotherapy at 6-12 weeks.	Moderate
HDL-c	4 (288)	Medium [2 trials with Jadad score<3]	Direct [Measured HDL-c in all trials]	Inconsistent [2 comparisons favor combination, 2 comparisons favor monotherapy, 1 comparison no difference]	Imprecise	Not detected None	Four studies with inconsistent results on HDL-c.	Insufficient

HDL = high-density lipoprotein; LDL = low-density lipoprotein; NA = not applicable

Combined Lipid-Modifying Therapy With Statin and Ezetimibe Versus Intensification of Statin Monotherapy

Study Characteristics

We included 40 trials (10,439 participants randomized to eligible arms – 5 studies with no baseline N by arm available) that compared intensification of statin monotherapy to lower potency statin therapy in combination with ezetimibe. The 40 trials were reported in 43 articles.[66-69,71-80,84-93,96-109,117,118,122,124,125] All studies were parallel arm RCTs, except one crossover RCT.[72] The studies were conducted in various geographic locations including Europe, Middle East, Asia, Latin America, North America, and some on multiple continents. Two trials did not report their location.[84,86] There were 17 single center trials[71-80,91,103,104,107,109,122,125], and 24 multicenter trials.[66-69,85,87-90,92,93,96,97,99,101,102,105,108,117,118,126] Most trials recruited patients with hyperlipidemia; [67-69,84,86,90,118,66,71-78,80,101,105,117,122]; however, several studies recruited only patients with preexisting CHD (n=14) [85,91-93,96-100,102-104,107,108,125] or patients with DM (n=6).[87-89 79,109,122] Treatment duration ranged from 4 to 24 weeks. Thirteen studies compared low potency statin in combination with ezetimibe to high potency statin monotherapy among general populations of patients with hyperlipidemia[66-69,71-78,80]; while there were no studies that evaluated this comparison among patients with preexisiting CHD and one study that evaluated this comparison among patients with DM.[79] Eleven studies compared mid potency statin in combination with ezetimibe to high potency statin monotherapy among general populations of patients with hyperlipidemia;[66-69,84,86,90,93,98,99,101,105] while 12 studies evaluated this comparison among patients with preexisiting CHD[85,91,92,96,97,100,102-104,107,108,125] and 4 studies evaluated this comparison among patients with DM. [87-89,106,109,124] Finally, 6 studies compared low potency statin in combination with ezetimibe to mid potency statin monotherapy among general populations with hyperlipidemia;[66-69,117,118] while no studies evaluated this comparison among patients with preexisiting CHD and one study evaluated this comparison among patients with DM[122] (Appendix E Evidence Tables).

Population Characteristics

Most participants were in their 50s-60s.[66-69,84-93,117,118,71-79,97-101,103-108,122,124] Two studies had participants whose mean age was in the 70s.[96,102] One trial reported a significant between group difference with respect to age, where the combination therapy arm was significantly older (p=0.04).[79] Female participants varied between trials, ranging from 12 percent to 70 percent. One study had only men.[71] Race was reported in most trials, and the majority were white (56 percent to 96 percent), with black, Hispanic, and Asian participants the next most common groups. Smoking status was reported in less than half of studies (n=17), and current smoking status varied between studies (range 6 percent to 69 percent).[68,84,90,91,93,118,73-78,96,100,102-104] Some trials included only diabetics (n=5)[79,87-89,109,122] and other trials had no diabetics (n=2).[71,77] DM status was reported in 23 other trials, and ranged from 0 percent to 67 percent of participants.[84,85,90-93,117,118,73-75,79,96,99-105,107,80,125] Prior CHD and revascularization events were not consistently reported across trials.

Interventions

Fourteen studies compared low potency statin in combination with ezetimibe to high potency statin monotherapy.[66-69,71-79,80] The statin monotherapy regimens included simvastatin, rosuvastatin, and atorvastatin. The combination therapy regimens included simvastatin and atorvastatin in combination with ezetimibe. Twenty-seven studies compared high potency statin monotherapy to mid potency statin in combination with ezetimibe.[66-69,84-93,106,124,96-105,107-109,125] The monotherapy regimens included simvastatin, rosuvastatin, and atorvastatin. The combination therapy included rosuvastatin, simvastatin and atorvastatin in combination with ezetimibe. Seven studies compared low potency statin in combination with ezetimibe to mid potency statin monotherapy.[66-69,117,118,122] The monotherapy regimens included simvastatin, rosuvastatin, fluvastatin and atorvastatin. The combination therapy included simvastatin, rosuvastatin, fluvastatin, lovastatin and atorvastatin in combination with ezetimibe.

Outcomes

Key Points

- **Long-Term Benefits**
    - Insufficient evidence for all potency comparisons.
- **Serious Adverse Events**
    - Insufficient evidence for all potency comparisons.
- **Surrogate Outcomes**
    - A low potency statin combined with ezetimibe is more effective than high potency statin monotherapy for lowering LDL-c (SOE: low).
    - A mid potency statin combined with ezetimibe is more effective than high potency statin monotherapy for lowering LDL-c (SOE: moderate).
    - A low potency statin combined with ezetimibe is more effective than mid potency statin monotherapy for lowering LDL-c (SOE: moderate).
    - A low potency statin combined with ezetimibe is more effective than high potency statin monotherapy for raising HDL-c (SOE: low).
    - A mid potency statin combined with ezetimibe is more effective than high potency statin monotherapy for raising HDL-c (SOE: low).
    - A low potency statin combined with ezetimibe is more effective than mid potency statin monotherapy for raising HDL-c (SOE: low).
- **Short-Term Side Effects**
    - There is insufficient evidence to compare the rates of adverse events for any potency comparison.
    - There is insufficient evidence to compare the rates of elevated liver transaminases for any potency comparison.
    - There is insufficient evidence to compare the rates of adverse musculoskeletal events for any potency comparison.
- **Adherence**
    - Insufficient evidence for all potency comparisons.
- **Subgroups**
    - CHD
        - Harms:
            - Insufficient evidence for all potency comparisons.
        - Benefits:
            - A mid potency statin combined with ezetimibe is more effective than high potency statin monotherapy for lowering LDL-c among CHD

patients (SOE: moderate). There is insufficient evidence within other potency comparisons.

- There is no difference between a mid potency statin combined with ezetimibe and high potency statin monotherapy for raising HDL-c among CHD patients (SOE: low). There is insufficient evidence within other potency comparisons.

- DM
  - Harms:
    - Insufficient evidence for all potency comparisons.
  - Benefits
    - A mid potency statin with ezetimibe is more effective than High potency statin monotherapy for lowering LDL-c among DM patients (SOE: moderate). There is insufficient evidence within other potency comparisons.
    - A mid potency statin combined with ezetimibe is more effective than high potency statin monotherapy for raising HDL-c among DM patients (SOE: moderate). There is insufficient evidence within other potency comparisons.

Long-Term Benefits and Serious Adverse Events (KQ 1)

Mortality

Low Potency Statin Combination Therapy Versus High Potency Statin Monotherapy

Two studies reported mortality.[67,68]. No deaths occurred in eligible arms in either trial. We graded the strength of evidence as insufficient.

Mid Potency Statin Combination Therapy Versus High Potency Statin Monotherapy

Six studies reported mortality.[67,68,86,98,99,101,105] Overall, mortality was very low with very few deaths. Monotherapy was favored in the studies that showed a difference between treatments; however, the between-group differences were not statistically significant (Table 9). Given the limited number of events, we are unable to compare the effect between groups and have graded the evidence as insufficient.

Table 9. Percentage of deaths in each arm of mid potency statin combination therapy versus high potency statin monotherapy

Author, Year	Regimen	Percentage of Deaths, Combination Therapy Arm	Percentage of Deaths, Monotherapy Arm
Zieve 2010[98], Ben-Yehuda 2011[99]	A10/E10 v A40	<1	<1
Foody 2010[101]	S20/E10 v A40	0.4	0.4
Foody 2010[101]	S20/E10 v A20	0.4	0
Robinson 2009[105]	S20/E10 v A40	0	0
Robinson 2009[105]	S20/E10 v A20	0	0
Bays 2004[67]	S20/E10 v A80	NR[a]	0
Bays 2004[67]	S20/E10 v S40	NR[a]	0
Davidson 2002[68]	S20/E10 v S80	1.72	NR
Davidson 2002[68]	S20/E10 v S40	1.72	NR
Catapano 2006[86]	S20/E10 v R40	0	0
Catapano 2006[86]	S20/E10 v R40	0	0

A = atorvastatin; E = ezetimibe; NR = not recorded; R = rosuvastatin; S = simvastatin;
[a]1 death in the combination therapy arm but cannot calculate proportion.

Low Potency Statin Combination Therapy Versus Mid Potency Statin Monotherapy

Two studies reported mortality.[67,68] No deaths occurred in eligible arms in either trial. We graded the strength of evidence as insufficient.

Acute Coronary Events

Low Potency Statin Combination Therapy Versus High Potency Statin Monotherapy

No studies reported on acute coronary events.

Mid Potency Statin Combination Therapy Versus High Potency Statin Monotherapy

One study reported on acute coronary events.[93] There was one fatal MI reported in the combination arm of that study (ezetimibe 10mg + atorvastatin 10mg). There were no fatal MIs reported in the monotherapy arm. We graded the strength of evidence as insufficient.

Low Potency Statin Combination Therapy Versus Mid Potency Statin Monotherapy

No studies reported on acute coronary events.

Cerebrovascular Disease

No studies reported on cerebrovascular events.

Revascularization Procedures

No studies reported on revascularization events.

Serious Adverse Events

Low Potency Statin Combination Therapy Versus High Potency Statin Monotherapy

No studies reported on serious adverse events.

Mid Potency Statin Combination Therapy Versus High Potency Statin Monotherapy

Three studies reported serious adverse events[93,98,99,101] (Table 10).

Table 10. Percentage of SAE in each arm of mid potency statin combination therapy versus high potency statin monotherapy

Author, Year	Regimen	N Analyzed by Group	% with SAE, Monotherapy	% With SAE, Combination Therapy	Calculated p-value
Foody, 2010 [101]	ATV 20mg SMV 20mg + EZE 10mg	258 256	1.2	3.1	0.22
Foody, 2010 [101]	ATV 40mg SMV 20mg + EZE 10mg	256 256	2.0	3.1	0.57
Stein, 2004 [93]	ATV 20mg ATV 10mg + EZE 10mg	525 526	2.8	3.9	0.45
Zieve, 2010; Ben-Yehuda, 2011 [98,99]	ATV 40mg ATV 10mg + EZE 10mg	316 305	2.7	2.9	0.86

As shown in Table 10, the percentage of patients in each arm experiencing an SAE in each arm was low overall. Two of these trials occurred in similar populations with similar interventions.[103,100,101] The study by Stein et al. (2004) was a 14-week trial that included different potency comparisons during different phases, of which only one period (weeks 0 to 4) were eligible for inclusion in this review.[95] However, the SAE were reported only during the course of the entire trial, and therefore, we could not determine what events, if any, occurred during the relevant period. We have elected to report the overall trial results from this study for completeness. Given that there were only two eligible trials, we did not perform meta-analysis and we graded the strength of evidence as insufficient.

Low Potency Statin Combination Therapy Versus Mid Potency Statin Monotherapy

One study reported serious adverse events.[117] The SAE rates were low overall (8% in combination therapy, and 5% in monotherapy) and the difference was not statistically significant (p-values calculated). We graded the strength of evidence as insufficient.

Surrogate Outcomes, Short-Term Side Effects and Adherence (KQ2)

Almost all included RCTs evaluated surrogate outcomes including LDL-c and HDL-c. In several RCTs, medication adherence and short-term side effects were evaluated including elevated liver transaminases and elevated creatinine phosphokinase. We identified no eligible non-randomized extensions of RCTs or FDA reports.

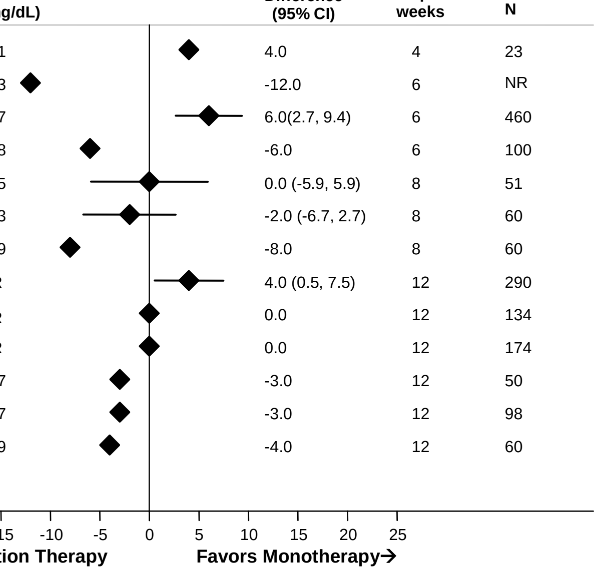
LDL-c

Low Potency Statin Combination Therapy Versus High Potency Statin Monotherapy

Thirteen studies evaluated LDL-c outcomes, with some trials reporting on multiple eligible arms for this potency comparison (20 arms).[66-69,71-78,80] Duration of therapy ranged from 6-12 weeks. As shown in Figure 3, six comparisons favored combination therapy for lowering LDL-c as compared to monotherapy (difference 2 percent to 12 percent).[71,73,75-78] Three comparisons favored monotherapy (difference 4 percent to 6 percent)[66,67,72] and four showed no difference.[68,69,74] Six studies had multiple arms comparing low potency statin combination therapy with different doses of high potency statin monotherapy.[66-69,77,80] Only the highest dose of statin monotherapy when the same statin was used is shown in the figure. Of the other comparison arms, six out of seven favored combination therapy (difference 3.4 percent to 8 percent).[67-69] One comparison favored monotherapy (difference 1.2 percent).[66] No studies reported LDL-c goal attainment.

We graded the strength of evidence as low. We considered performing meta-analysis, however, few (31%) of the trials had a calculable standard error for the difference in difference, therefore, we did not feel that a meta-analysis would be an accurate pooling of the available literature (Figure 3).

Figure 3. Mean difference in percent LDL change from baseline to time point comparing low potency combination therapy with ezetimibe to high potency monotherapy



Author, Year	Statin Monotherapy	Combination Therapy	Monotherapy Baseline LDL-c (mg/dL)	Combination Baseline LDL-c (mg/dL)	Between Group Difference (95% CI)	Timepoint weeks	N
Araujo 2010	SMV 80mg	EZE10mg+SMV10mg	206	201	4.0	4	23
Ahmed 2008	ATV 20mg	EZE10mg+SMV10mg	173	173	-12.0	6	NR
Ballantyne 2005	ATV 80mg	EZE10mg+SMV10mg	183	177	6.0(2.7, 9.4)	6	460
Florentin 2011	SMV 40mg	EZE10mg+SMV10mg	172	178	-6.0	6	100
Her 2013	RSV 10mg	EZE5mg+ATV5mg	163	165	0.0 (-5.9, 5.9)	8	51
Lee 2011	ATV 20mg	EZE5mg+ATV5mg	164	163	-2.0 (-6.7, 2.7)	8	60
Lee 2012	ATV 20mg	EZE5mg+ATV5mg	161	159	-8.0	8	60
Bays 2004	SMV 80mg	EZE10mg+SMV10mg	NR	NR	4.0 (0.5, 7.5)	12	290
Davidson 2002	SMV 80mg	EZE10mg+SMV10mg	NR	NR	0.0	12	134
Goldberg 2004	SMV 80mg	EZE10mg+SMV10mg	NR	NR	0.0	12	174
Liberopoulos 2013	SMV 40mg	EZE10mg+SMV10mg	176	177	-3.0	12	50
Moutzouri 2011	RSV 10mg	EZE10mg+SMV10mg	182	177	-3.0	12	98
Moutzouri 2012	SMV 80mg	EZE10mg+SMV10mg	174	179	-4.0	12	60

ATV = atorvastatin; SMV = simvastatin; NR = not reported
Note: For diamonds without confidence intervals, SE/SD could not be calculated.

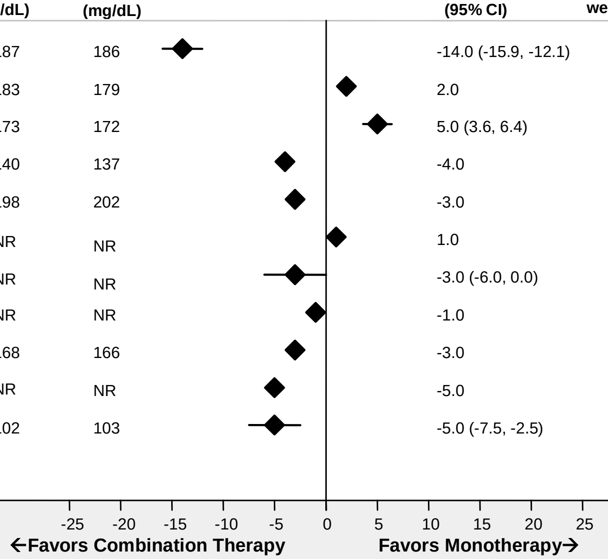
<u>Mid</u> Potency Statin Combination Therapy Versus <u>High</u> Potency Statin Monotherapy

Eleven studies evaluated LDL-c outcomes with some trials reporting on multiple eligible arms for this potency comparison (22 arms).[66-69,84,86,90,93,98,101,105,99] As shown in Figure 4, eight comparisons favored combination therapy for lowering LDL-c as compared to monotherapy (difference 3% to 14%).[67,69,84,90,93,98,99,101,105] Duration of therapy ranged from 4 to 12 weeks. Two comparisons favored monotherapy (difference 2% to 5%).[66,86] and two comparisons were neutral.[68,84] Eight studies had multiple arms comparing mid potency statin combination therapy with different doses of high potency statin monotherapy.[66-69,84,86,101,105] Only the highest dose of statin monotherapy is shown in the figure 3. Of the other comparison arms, ten out of eleven favored combination therapy (difference 2.3% to 11.3%)[66,67,69,84,101,105], and the other was neutral (0.8% difference).[68] In addition, 3 studies (5 comparisons) reported on attainment of ATP III LDL-c goals.[98,99,101,105] In five comparisons, more patients in the combination therapy group achieved LDL target (difference 7.5% to 25.0%).[98,99,101,105]

We graded the strength of evidence as moderate. We considered performing meta-analysis, however, few (30%) of the trials had a calculable standard error for the difference in difference, therefore, we did not feel that a meta-analysis would be an accurate pooling of the available literature.

Figure 4. Mean difference in percent LDL change from baseline to time point comparing mid potency combination therapy with ezetimibe to high potency monotherapy

Author, Year	Statin Monotherapy	Combination Therapy	Monotherapy Baseline LDL-c (mg/dL)	Combination Baseline LDL-c (mg/dL)	Between Group Difference (95% CI)	Timepoint weeks	N
Stein 2004	ATV 20mg	EZE10mg+ATV10mg	187	186	-14.0 (-15.9, -12.1)	4	596
Ballantyne 2005	ATV 80mg	EZE10mg+SMV20mg	183	179	2.0	6	463
Catapano 2006	RSV 40mg	EZE10mg+SMV20mg	173	172	5.0 (3.6, 6.4)	6	951
Robinson 2009	ATV 40mg	EZE10mg+SMV20mg	140	137	-4.0	6	436
McKenney 2007	RSV 20mg	EZE10mg+SMV20mg	198	202	-3.0	8	145
Ballantyne 2003	ATV 80mg	EZE10mg+ATV10mg	NR	NR	1.0	12	NR
Bays 2004	SMV 80mg	EZE10mg+SMV20mg	NR	NR	-3.0 (-6.0, 0.0)	12	290
Davidson 2002	SMV 80mg	EZE10mg+SMV20mg	NR	NR	-1.0	12	121
Foody 2010	ATV 40mg	EZE10mg+SMV20mg	168	166	-3.0	12	471
Goldberg 2004	SMV 80mg	EZE10mg+SMV20mg	NR	NR	-5.0	12	173
Zieve 2010, Ben-Yehuda 2011	ATV 40mg	EZE10mg+ATV10mg	102	103	-5.0 (-7.5, -2.5)	12	1025



ATV = atorvastatin; NR = not reported; SMV = simvastatin

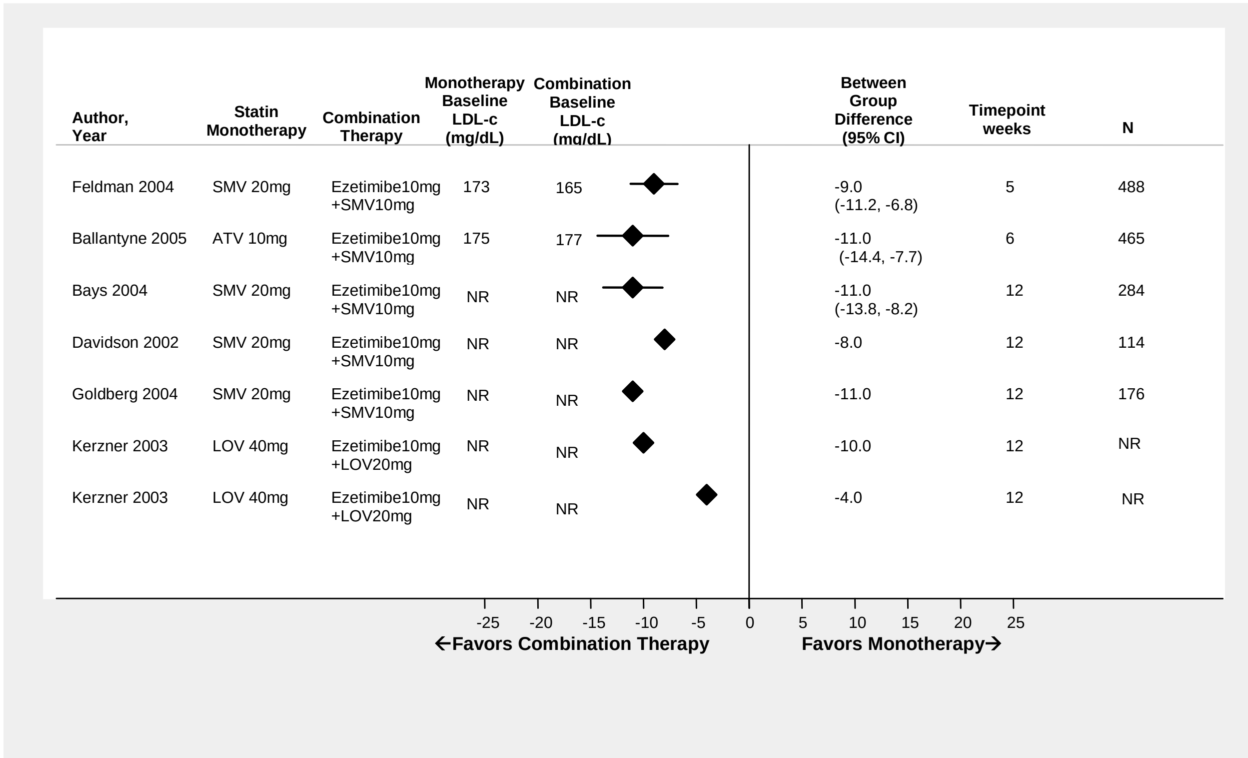
Note: For diamonds without confidence intervals, SE/SD could not be calculated.

<u>Low</u> Potency Statin Combination Therapy Versus <u>Mid</u> Potency Statin Monotherapy

Six studies evaluated LDL-c outcomes with some trials reporting on multiple eligible arms for this potency comparison (7 comparisons).[66-69,117,118] All comparisons favored combination therapy for lowering LDL-c as compared to monotherapy (difference 3% to 11.3%).[66-69,117,118] Duration of therapy ranged from 5 to 12 weeks. No studies reported LDL-c goal attainment.

The results of all studies favored mid potency statin in combination with ezetimibe for lowering LDL-c (Figure 5). We graded the strength of evidence as moderate. We considered performing meta-analysis, however, few (43%) of the trials had a calculable standard error for the difference in difference, therefore, we did not feel that a meta-analysis would be an accurate pooling of the available literature.

Figure 5. Mean difference in percent LDL change from baseline to time point comparing low potency combination therapy with ezetimibe to mid potency monotherapy



ATV = atorvastatin; LOV = lovastatin; NR = not reported; RSV = rosuvastatin; SMV = simvastatin
Note: For diamonds without confidence intervals, SE/SD could not be calculated.

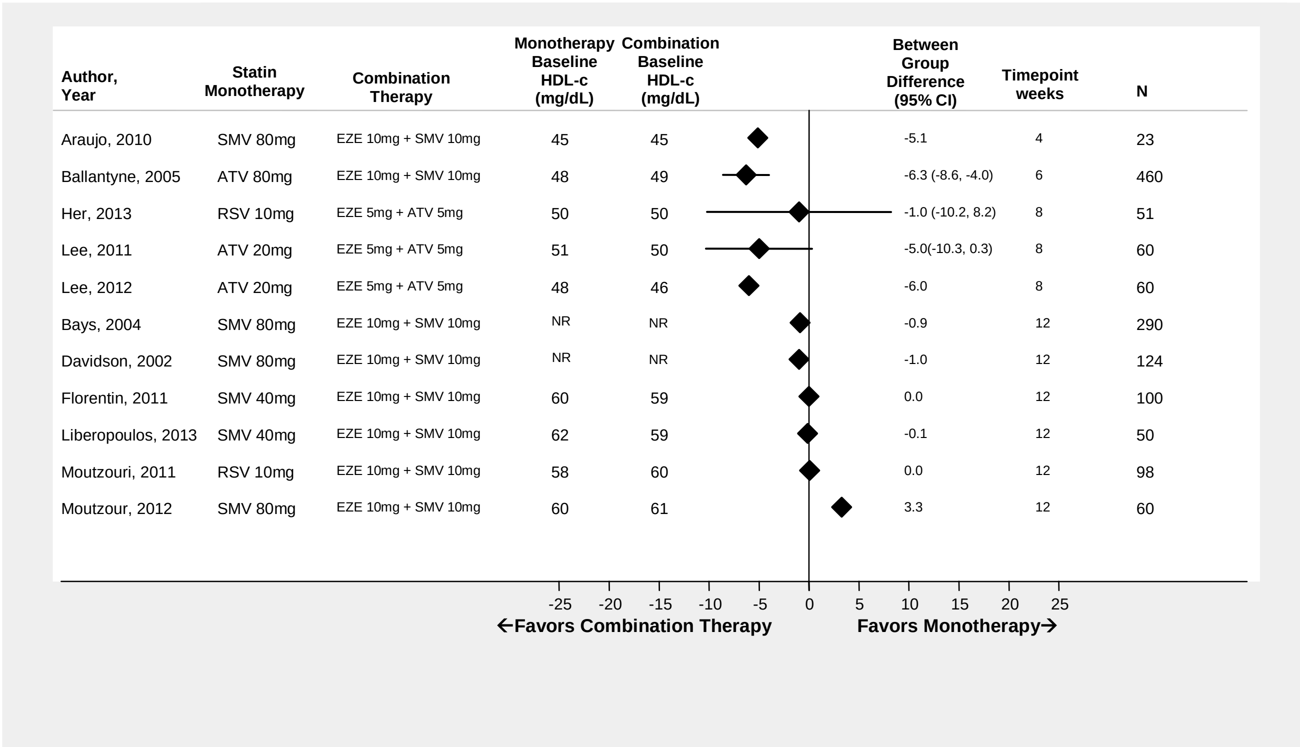
HDL-c

<u>Low</u> Potency Statin Combination Therapy Versus <u>High</u> Potency Statin Monotherapy

Eleven studies (sixteen comparisons) evaluated HDL-c.[66-68,72-78,80] As shown in Figure 6, three comparisons favored combination therapy for raising HDL-c as compared to monotherapy (difference 5.14% to 6.3%).[66,72,75] Duration of therapy ranged from 4 to 12 weeks. Six comparisons were neutral [66-68,73,74,76,80] and one comparison favored monotherapy (difference 3.28%)[78] Three studies had multiple arms comparing low potency statin combination therapy with different doses of high potency statin monotherapy.[66-68] Only the highest dose of statin monotherapy is shown in the figure. Of the other comparison arms, four out of five favored combination therapy (difference 2.6% to 3.9%)[66,68,80] and one was neutral (0.5% difference).[67,71]

We graded the strength of evidence as low (Table 11). We considered performing meta-analysis, however, few (27%) of the trials had a calculable standard error for the difference in difference, therefore, we did not feel that a meta-analysis would be an accurate pooling of the available literature (Figure 7).

Figure 6. Mean difference in percent HDL change from baseline to time point comparing low potency combination therapy with ezetimibe to high potency monotherapy



ATV = atrovastatin; NR = not reported; SMV = simvastatin

Note: For diamonds without confidence intervals, SE/SD could not be calculated.

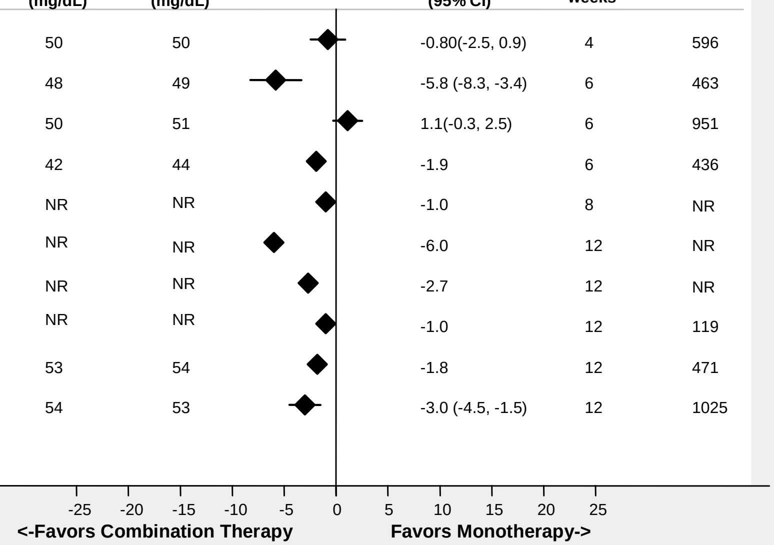
<u>Mid</u> Potency Statin Combination Therapy Versus <u>High</u> Potency Statin Monotherapy

Ten studies (21 comparisons) evaluated HDL-c.[66-69,84,86,90,93,98,99,101,105] Six studies favored combination therapy for raising HDL-c as compared to monotherapy (difference 1.8% to 6%).[66,67,69,84,98,99,101,105] Four studies were neutral.[93,68,86,90] Duration of therapy ranged from 4 to 12 weeks. Seven studies had multiple arms comparing low potency statin combination therapy with different doses of high potency statin monotherapy.[66,66-68,86,101,105] Only the highest dose of statin monotherapy is shown i`n the figure. Of the other comparison arms, ten out of eleven favored combination therapy (difference 1.2% to 5%)[66-68,84,86,93] and two were neutral (difference 0.8 percent to 1.1 percent).[101,105]

We graded the strength of evidence as low (Table 12). We considered performing meta-analysis, however, few (44%) of the trials had a calculable standard error for the difference in difference, therefore, we did not feel that a meta-analysis would be an accurate pooling of the available literature.

Figure 7. Mean difference in percent HDL change from baseline to time point comparing mid potency combination therapy with ezetimibe to high potency statin monotherapy

Author, Year	Statin Monotherapy	Combination Therapy	Monotherapy Baseline HDL-c (mg/dL)	Combination Baseline HDL-c (mg/dL)	Between Group Difference (95% CI)	Timepoint weeks	N
Stein 2004	ATV 20mg	Ezetimibe 10mg +ATV10mg	50	50	-0.80(-2.5, 0.9)	4	596
Ballantyne 2005	ATV 80mg	Ezetimibe 10mg +SMV20mg	48	49	-5.8 (-8.3, -3.4)	6	463
Catapano 2006	RSV 40mg	Ezetimibe 10mg +SMV20mg	50	51	1.1(-0.3, 2.5)	6	951
Robinson 2009	ATV 40mg	Ezetimibe 10mg +SMV20mg	42	44	-1.9	6	436
McKenney 2007	RSV 20mg	Ezetimibe 10mg +SMV20mg	NR	NR	-1.0	8	NR
Ballantyne 2003	ATV 80mg	Ezetimibe 10mg +ATV10mg	NR	NR	-6.0	12	NR
Bays 2004	SMV 80mg	Ezetimibe 10mg +SMV20mg	NR	NR	-2.7	12	NR
Davidson 2002	SMV 80mg	Ezetimibe 10mg +SMV20mg	NR	NR	-1.0	12	119
Foody 2010	ATV 40mg	Ezetimibe 10mg +SMV20mg	53	54	-1.8	12	471
Zieve 2010, Ben-Yehuda 2011	A20/A40mg	Ezetimibe 10mg +ATV10mg	54	53	-3.0 (-4.5, -1.5)	12	1025



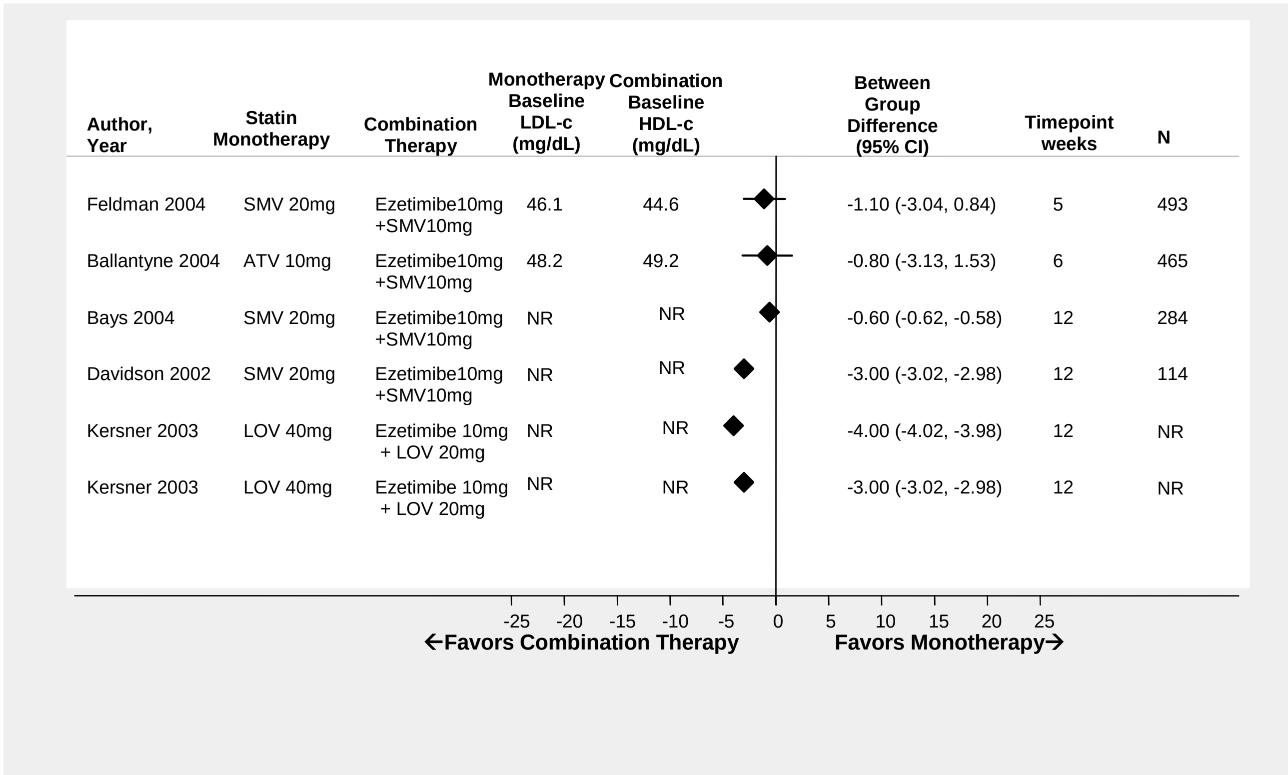
Mean Difference in Percent HDL Change from Baseline to Timepoint Comparing Mid Potency Combination Therapy with Ezetimibe to High Potency Statin Monotherapy

ATV = atorvastatin; EZE = ezetimibe; NR = not reported; RSV = rosuvastatin; SMV = simvastatin
Note: For diamonds without confidence intervals, SE/SD could not be calculated.

<u>Low</u> Potency Statin Combination Therapy Versus <u>Mid</u> Potency Statin Monotherapy

Six studies evaluated HDL-c.[66-69,117,118] Three studies favored combination therapy for raising HDL-c as compared to monotherapy (difference 3% to 4%) (Figure 8).[68,118] Both comparisons in the Kersner et al study [118] were included in the figure because there were different low potency statin combination regimens used. Three studies were neutral (difference 0.05% to 1.1%).[66,67,117] We graded the strength of evidence as low (Table 13). Only one trial reported or provided sufficient information for us to calculate SE for the HDL-c difference in differences, and therefore, we did not perform meta-analysis.

Figure 8. Mean difference in percent HDL change from baseline to time point comparing low potency combination therapy with ezetimibe to mid potency statin monotherapy



ATV = atrovastatin; LOV = lovastatin; NR = not reported; SMV = simvastatin
Note: For diamonds without confidence intervals, SE/SD could not be calculated.

Total Cholesterol: HDL

Low Potency Statin Combination Therapy Versus High Potency Statin Monotherapy

One study reported total cholesterol:HDL ratio.[67] The effects on lowering total cholesterol:HDL were inconsistent and showed little to no absolute difference between combination therapy and statin monotherapy.

Mid Potency Statin Combination Therapy Versus High Potency Statin Monotherapy

Seven studies (12 arms) reported total cholesterol:HDL ratio.[68,69,84,86,90,93,98,99,101,105] Most comparisons favored monotherapy for lowering total cholesterol:HDL as compared to combination therapy (difference 1.6% to 11.8%).[68,69,84,90 ,93,98,99,101,105] Duration of therapy ranged from 6-12 weeks. However, two comparisons favored combination therapy (difference 1.1% to 4.2%).[86]

Low Potency Statin Combination Therapy Versus Mid Potency Statin Monotherapy

No studies reported total cholesterol:HDL ratio.

Atherosclerosis

No studies reported on atherosclerosis

Adherence

Low Potency Statin Combination Therapy Versus High Potency Statin Monotherapy

No studies reported adherence.

Mid Potency Statin Combination Therapy Versus High Potency Statin Monotherapy

One studies reported on adherence.[90] One study favored combination therapy with 98 percent adherence among combination therapy patients and 84 percent adherence among monotherapy patients (defined as returning 75 and 125% of dispensed tablets).[90]

Low Potency Statin Combination Therapy Versus Mid Potency Statin Monotherapy

No studies reported adherence.

Any Adverse Event

Low Potency Statin Combination Therapy Versus High Potency Statin Monotherapy

No studies reported adverse events.

Mid Potency Statin Combination Therapy Versus High Potency Statin Monotherapy

Three studies reported adverse events.[93,98,99,101] In one comparison[98,99], more patients in the monotherapy arm experienced at least one adverse event (difference 3%). In three comparisons, more patients in the combination therapy arm experienced at least one adverse event (difference 2.5% to 5%).[93,101]

Low Potency Statin Combination Therapy Versus Mid Potency Statin Monotherapy

One study reported adverse events.[117] More participants in the monotherapy group had an adverse event (66%) than the combination therapy group (56%) (p=0.02).

Withdrawal Due to Adverse Events

<u>Low</u> Potency Statin Combination Therapy Versus <u>High</u> Potency Statin Monotherapy

One study reported withdrawals due to adverse events.[68] In one monotherapy arm (simvastatin 40mg), 3 percent of patients withdrew due to adverse events. No participants in the combination arm or other monotherapy arm (simvastatin 80mg) withdrew due to adverse events.

<u>Mid</u> Potency Statin Combination Therapy Versus <u>High</u> Potency Statin Monotherapy

Three studies reported withdrawals due to adverse events (8 arms).[68,98,99,101] In one comparison, there was no difference in withdrawal due to adverse events between the combination therapy and monotherapy arms[68] with no event in either arm. In three comparisons, more patients in the combination therapy group withdrew due to adverse event (difference 1% to 2.3%).[98,99,101] In one comparison, more patients in the monotherapy group withdrew due to AE (difference 3.3 percent).[68]

<u>Low</u> Potency Statin Combination Therapy Versus <u>Mid</u> Potency Statin Monotherapy

Two studies reported withdrawals due to adverse events.[68,117] The combination arms in both studies had fewer withdrawals due to adverse events than the monotherapy arms (difference range 1% to 11% favoring combination therapy).

Cancer

No studies reported on cancer.

Elevated Liver Transaminases

<u>Low</u> Potency Statin Combination Therapy Versus <u>High</u> Potency Statin Monotherapy

Three studies reported on elevated liver transaminases (AST and/or ALT > 3 times ULN).[74,75,80] No participants experienced elevated liver enzymes.

<u>Mid</u> Potency Statin Combination Therapy Versus <u>High</u> Potency Statin Monotherapy

Six studies reported on elevated liver transaminases (AST and/or ALT > 3 times ULN).[86,90,93,98,99,101,105] Overall, few patients experienced elevated transaminases in any arm. In three comparisons, more patients in the combination therapy group experienced elevated liver transaminases (difference 0.2% to 1.4%).[86,90,101] In four comparisons, more patients in the monotherapy group experienced elevated liver transaminases (difference 0.7% to 1.8%).[93,101,105]

One comparison[86] (rosuvastatin 40 vs. simvastatin 20/ ezetimibe 10) showed no difference in the proportion of patients with elevated liver transaminases.

<u>Low</u> Potency Statin Combination Therapy Versus <u>Mid</u> Potency Statin Monotherapy

One study reported on elevated liver transaminases.[117] Overall, few patients experienced elevated transaminases in this trial (0% in monotherapy and 0.4% in combination therapy).

Musculoskeletal Adverse Events

<u>Low</u> Potency Statin Combination Therapy Versus <u>High</u> Potency Statin Monotherapy

Three studies reported on CPK > 10 times ULN.[74,75,80] No patients in any eligible arm experienced CPK elevations. One reported on myalgia[80], with one reported case of myalgia in the monotherapy arm.

Mid Potency Statin Combination Therapy Versus High Potency Statin Monotherapy

Six studies reported on CPK > 10 times ULN.[86,90,93,98,99 ,101,105] Overall, few patients experienced CPK elevations regardless of treatment arm. In two comparisons, more patients in the combination therapy group experienced CPK > 10x ULN (difference 0.4% in both).[105] In two comparisons, more patients in the monotherapy group experienced CPK > 10x ULN (difference 0.1% to 0.3%).[93,86] Four comparisons showed no difference.[86,90,101] Three studies reported on myalgia.[86,93,98,99] There was little to no difference between treatment arms with respect to reports of myalgia (difference range 0% to 1%).

Low Potency Statin Combination Therapy Versus Mid Potency Statin Monotherapy

One study reported on CPK > 10 times ULN.[117] No participants in the combination arm experienced CPK elevations, and only 1 percent of participants in the monotherapy arm had CPK elevations. No studies reported on myalgia.

New Onset Diabetes Mellitus

No studies reported on new-onset diabetes mellitus.

Acute Kidney Injury

No studies reported on acute kidney injury.

Subgroups of Patients (KQ 3)

There were many studies involving participants with DM and CHD. There were few studies making subgroup comparisons by gender (female), race (Black, Hispanic, and Asian), or age (> 75 years old). Surrogate clinical markers were commonly reported by subgroup; however, serious adverse events and mortality were not commonly reported by subgroup (Appendix Table E60).

Patients With Preexisting Coronary Heart Disease

Overall, 12 studies included analyses of patient populations with preexisiting CHD. No studies compared low potency statin in combination with ezetimibe to high potency statin monotherapy among patients with preexisting CHD (Table 14). Twelve studies compared mid potency statin in combination with ezetimibe to high potency statin monotherapy among patients with preexisiting CHD.[85,91,92,96,97,100,102-104,107,108,125]

No studies compared low potency statin in combination with ezetimibe to mid potency statin monotherapy among patients with preexisting CHD.

Mortality

Low potency statin combination therapy versus high potency statin monotherapy. No studies reported mortality among patients with preexisting CHD.

Mid potency statin combination therapy versus high potency statin monotherapy. Three studies reported mortality among patients with preexisting CHD.[85,92,108] No deaths occurred in these studies. We graded the strength of evidence as insufficient (Table 15**).**

Low potency statin combination therapy versus mid potency statin monotherapy. No studies reported mortality among patients with preexisting CHD.

Acute Coronary Events

Low potency statin combination therapy versus high potency statin monotherapy. No studies reported acute coronary events among patients with preexisting CHD.

Mid potency statin combination therapy versus high potency statin monotherapy. One study reported on acute coronary events, specifically fatal MI, among patients with preexisting CHD.[103] No fatal MI occurred in the monotherapy arm and one fatal MI occurred in the combination therapy arm. We graded the strength of evidence as insufficient (Table 15).

Low potency statin combination therapy versus mid potency statin monotherapy. No studies reported acute coronary events among patients with preexisting CHD.

Cerebrovascular Events

Low potency statin combination therapy versus high potency statin monotherapy. No study reported cerebrovascular events among patients with preexisting CHD.

Mid potency statin combination therapy versus high potency statin monotherapy. One study reported cerebrovascular events among patients with preexisting CHD, specifically transient ischemic attack (TIA).[108] One TIA occurred in the monotherapy arm (2%) and no events occurred in the combination arm, which was not a significant difference.

Low potency statin combination therapy versus mid potency statin monotherapy. No study reported cerebrovascular events among patients with preexisting CHD.

Revascularization Procedures

No studies reported on revascularization procedures among patients with preexisting CHD.

Serious Adverse Events

Low potency statin combination therapy versus high potency statin monotherapy. No study reported serious adverse events among patients with preexisting CHD.

Mid potency statin combination therapy versus high potency statin monotherapy. Three studies reported serious adverse events among patients with preexisting CHD.[85,97,108] Overall, the numbers of events were low. In two comparisons, more combination therapy patients experienced SAE (difference 0.02% to 1.4%).[85,97] In one comparison, more monotherapy group patients experienced SAE (difference 1.7 percent). We graded the strength of evidence as insufficient (Table 15).

Low potency statin combination therapy versus mid potency statin monotherapy. No study reported serious adverse events among patients with preexisting CHD.

LDL-c

Low potency statin combination therapy versus high potency statin monotherapy. No studies reported on LDL-c outcomes among patients with preexisting CHD. We graded the strength of evidence as insufficient (Table 14).

Mid potency statin combination therapy versus high potency statin monotherapy. Twelve studies reported on LDL-c outcomes among patients with preexisting CHD.[85,91,92,96,97,100,102-104,107,108,125] In nine comparisons, combination therapy lowered LDL more than monotherapy (difference 5% to 15%).[85,91,92,97,102,107,108] Three studies were neutral (difference 1% to 3.1%)[96,100,104] and one study favored monotherapy.[103]

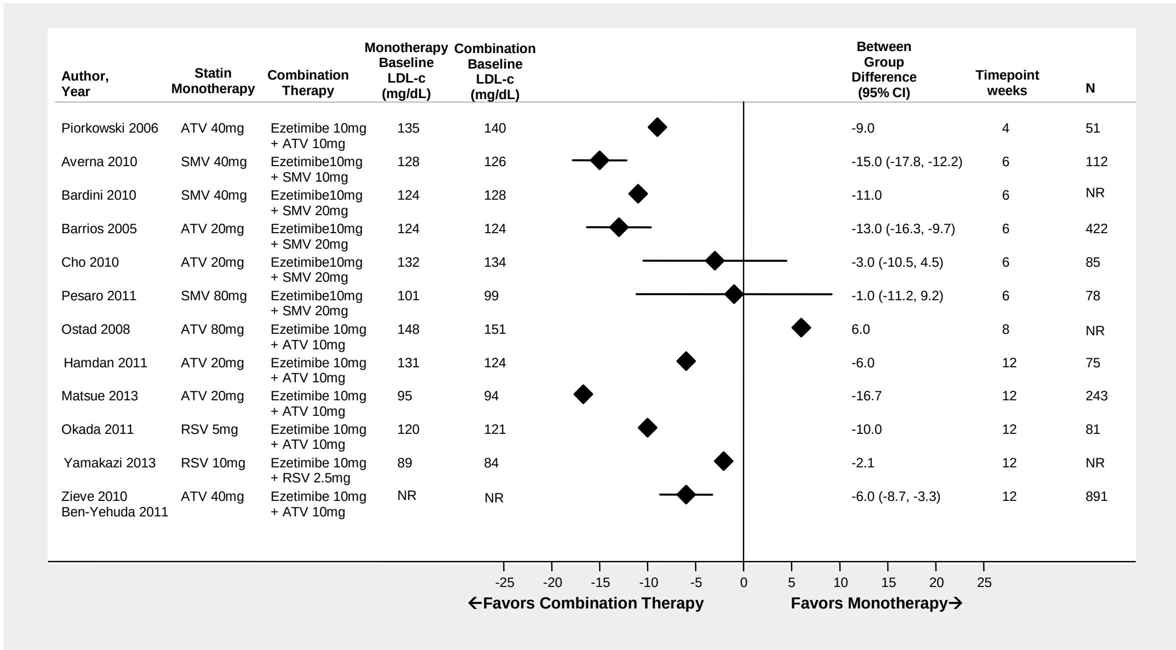
In addition, one study reported LDL-c change among female participants with preexisting CHD.[85] This study favored combination therapy for LDL-c reduction in female participants with CHD. Mean percent change in the monotherapy group was 21 percent, while mean percent change in the combination therapy group was 34 percent.

Four studies reported attainment of LDL-c < 100 mg/dL among patients with preexisting CHD.[85,91,92,108] Most comparisons favored combination therapy over monotherapy for attaining this LDL-c goal (difference range 13% to 49% favoring combination therapy), which was a statistically significant difference in 3 trials.[85,92,108]

We graded the strength of evidence as moderate (Table 15).

Summary estimates from meta-analysis are not reported due to high heterogeneity (I^2=94.5%) (Figure 9).

Figure 9. Mean difference in percent LDL-c change from baseline to time point comparing mid potency combination therapy with ezetimibe to high potency monotherapy among CHD patients



ATV = atorvastatin; NR = not reported; SMV = simvastatin

Note: For diamonds without confidence intervals, SE/SD could not be calculated.

Low potency statin combination therapy versus mid potency statin monotherapy. No studies reported on LDL-c outcomes among patients with preexisting CHD. We graded the strength of evidence as insufficient (Table 16).

HDL-c

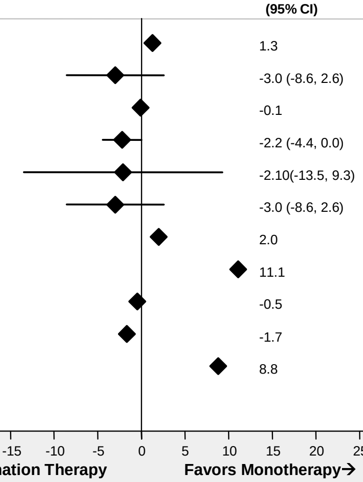
Low potency statin combination therapy versus high potency statin monotherapy. No studies reported on HDL-c among patients with preexisting CHD.

Mid potency statin combination therapy versus high potency statin monotherapy. Eleven studies reported HDL-c among patients with preexisting CHD.[85,91,97,100,102-104,107,108,96,125] One study favored combination therapy (difference 7.33%).[102] One study favored monotherapy (difference 6%).[107] However, most results were neutral (difference 0.1% to 5.6%, NS).[85,9197,100,103,104,108] Given that the results were inconsistent with respect to raising HDL-c among patients with preexisting CHD (Figure 10), we graded the strength of evidence as low for no effect (Table 15). We considered performing meta-analysis, however, few (45%) of the trials had a calculable standard error for the difference in difference, therefore, we did not feel that a meta-analysis would be an accurate pooling of the available literature.

Low potency statin combination therapy versus mid potency statin monotherapy. No studies reported on HDL-c among patients with preexisting CHD. We graded the strength of evidence as insufficient (Table 16).

Figure 10. Mean difference in percent HDL change from baseline to time point comparing mid potency combination therapy with ezetimibe to high potency statin monotherapy in patients with CHD

Author, Year	Statin Monotherapy	Combination Therapy	Monotherapy Baseline HDL-c (mg/dL)	Combination Baseline HDL-c (mg/dL)	Between Group Difference (95% CI)	Timepoint weeks	N
Piorkowski 2007	ATV 40mg	Ezetimibe 10mg + ATV 10mg	51	54	1.3	4	51
Averna 2010	SMV 40mg	Ezetimibe10mg + SMV 10mg	49	51	-3.0 (-8.6, 2.6)	6	112
Bardini 2010	SMV 40mg	Ezetimibe10mg + SMV 20mg	NR	NR	-0.1	6	87
Barrios 2005	ATV 20mg	Ezetimibe10mg + SMV 20mg	56	54	-2.2 (-4.4, 0.0)	6	422
Cho 2010	ATV 20mg	Ezetimibe10mg + SMV 20mg	46	45	-2.10(-13.5, 9.3)	6	85
Pesaro 2011	SMV 80mg	Ezetimibe10mg + SMV 20mg	45	42	-3.0 (-8.6, 2.6)	6	78
Ostad 2008	ATV 80mg	Ezetimibe 10mg + ATV 10mg	52	58	2.0	8	NR
Hamdan 2011	ATV 20mg	Ezetimibe 10mg + ATV 10mg	35	35	11.1	12	79
Matsue 2013	ATV 20mg	Ezetimibe 10mg + ATV 10mg	51	52	-0.5	12	243
Okada 2011	RSV 5mg	Ezetimibe 10mg + ATV 10mg	50	53	-1.7	12	81
Yamakazi 2013	RSV 10mg	Ezetimibe 10mg + RSV 2.5mg	46	50	8.8	12	NR



ATV = atorvastatin; NR = not reported; SMV = simvastatin
Note: For diamonds without confidence intervals, SE/SD could not be calculated.

Total Cholesterol: HDL-c

Low potency statin combination therapy versus high potency statin monotherapy. No study reported total cholesterol: HDL-c ratio among patients with preexisting CHD.

Mid potency statin combination therapy versus high potency statin monotherapy. One study reported total cholesterol:HDL-c ratio among patients with preexisting CHD.[85] Combination therapy reduced total cholesterol: HDL by 9 percent more than monotherapy.

Low potency statin combination therapy versus mid potency statin monotherapy. No study reported total cholesterol: HDL-c ratio among patients with preexisting CHD.

Atherosclerosis

No study reported on atherosclerosis measures among patients with preexisting CHD.

Adherence

Low potency statin combination therapy versus high potency statin monotherapy. No study reported on adherence among patients with preexisting CHD.

Mid potency statin combination therapy versus high potency statin monotherapy. Two studies reported on adherence among patients with preexisting CHD.[97,100] One study[100] showed similar adherence between groups, with adherence reported at >99 percent in both groups, although the authors did not provide detail on how they assessed adherence. The other study[97] assessed adherence by tablet count and showed a slight advantage to combination therapy (difference 1.5%).

Low potency statin combination therapy versus mid potency statin monotherapy. No study reported on adherence among patients with preexisting CHD.

Any Adverse Event

Low potency statin combination therapy versus high potency statin monotherapy. No study reported on occurrence of any adverse events among patients with preexisting CHD.

Mid potency statin combination therapy versus high potency statin monotherapy. Three studies reported on the occurrence of any adverse events among patients with preexisting CHD.[85,97,108] In one comparison, there was no difference between the two groups.[108] In two comparisons, more monotherapy group patients experienced this outcome (difference 3.9% to 7.5%).[85,97]

Low potency statin combination therapy versus mid potency statin monotherapy. No study reported on occurrence of any adverse events among patients with preexisting CHD.

Withdrawal Due to Adverse Events

Low potency statin combination therapy versus high potency statin monotherapy. No study reported on withdrawals due to adverse events among patients with preexisting CHD.

Mid potency statin combination therapy versus high potency statin monotherapy. Five studies reported on withdrawals due to adverse events among patients with preexisting CHD.[85,97,103,107,108] In all comparisons, more monotherapy patients experienced this outcome (difference 1.4% to 17.9%).

Low potency statin combination therapy versus mid potency statin monotherapy. No study reported on withdrawals due to adverse events among patients with preexisting CHD.

Elevated Liver Transaminases

Low potency statin combination therapy versus high potency statin monotherapy. No study reported on elevated liver transaminases among patients with preexisting CHD.

Mid potency statin combination therapy versus high potency statin monotherapy. Six studies reported elevated liver transaminases (AST and/or ALT > 3 times ULN) among patients with preexisting CHD.[85,97,100,104,107,108] In four comparisons, there was no difference in this outcome. In one comparison, more combination therapy patients experienced LFT elevation (difference 0.5%)[85]; in another comparison more monotherapy patients experienced this adverse event (difference 2.6%)[100]

Low potency statin combination therapy versus mid potency statin monotherapy. No study reported on elevated liver transaminases among patients with preexisting CHD.

Musculoskeletal Adverse Events

Low potency statin combination therapy versus high potency statin monotherapy. No study reported on elevation in CPK or cases of myalgia among patients with preexisting CHD.

Mid potency statin combination therapy versus high potency statin monotherapy. Four studies reported on elevations in CPK > 10 times ULN among patients with preexisting CHD.[85,97,100,108] No participant experienced this event in any trial. One study reported on occurrence of myalgia among patients with preexisting CHD.[104] There were no reported cases of myalgia in either group.

Low potency statin combination therapy versus mid potency statin monotherapy. No study reported on elevation in CPK or cases of myalgia among patients with preexisting CHD.

Cancer

No study reported on cancer among patients with preexisting CHD.

New Onset Diabetes Mellitus

No study reported on cases of new onset diabetes mellitus among patients with preexisting CHD.

Acute Kidney Injury

No study reported on cases of acute kidney injury among patients with preexisting CHD.

Patients With Diabetes Mellitus

One study compared low potency statin therapy in combination with ezetimibe to high potency statin monotherapy in patients with DM.[79] Four studies compared mid potency statin in combination with ezetimibe to high potency statin monotherapy in patients with DM.[87-89,106,109,124] One study compared low potency statin in combination with ezetimibe to mid potency statin monotherapy in patients with DM.[122]

Mortality

Low potency statin combination therapy versus high potency statin monotherapy. No study reported on mortality among patients with DM (Table 17).

Mid potency statin combination therapy versus high potency statin monotherapy. Two studies reported mortality among patients with DM.[87,89,106,124] Events were low. Two arms favored combination therapy, with 0.4 percent deaths in the monotherapy arm compared with 0 deaths in the combination arm and 0.5 percent deaths in the monotherapy arm compared with 0 deaths in the combination arm. P-value was not reported in one study[87] and was reported as non-significant in the other.[89,106,124] We graded the strength of evidence as insufficient (Table 18).

Low potency statin combination therapy versus mid potency statin monotherapy. No study reported on mortality among patients with DM.

Acute Coronary Events

No study reported on acute coronary events among patients with DM.

Cerebrovascular Disease

No study reported on cerebrovascular events among patients with DM.

Revascularization Procedures

No study reported on revascularization procedures among patients with DM.

Serious Adverse Events

Low potency statin combination therapy versus high potency statin monotherapy. No study reported on serious adverse events among patients with DM.

<u>Mid</u> potency statin combination therapy versus <u>high</u> potency statin monotherapy. Five studies (six arms) reported serious adverse events among patients with DM.[87,88,97,101,109] In four comparisons, there were more SAEs in the combo therapy group (difference 0.02% to 3.9%). In one comparison, there were more SAEs in the monotherapy group (difference 1.8%). One study reported no SAEs in either arm[109]. We graded the strength of evidence as insufficient (Table 18).

<u>Low</u> potency statin combination therapy versus <u>mid</u> potency statin monotherapy. No study reported on serious adverse events among patients with DM.

LDL-c

<u>Low</u> potency statin combination therapy versus <u>high</u> potency statin monotherapy. One study reported LDL-c outcomes among patients with DM.[79] Monotherapy therapy lowered LDL-c 2 percent more than combination therapy. No studies reported LDL-c goal attainment. We graded the strength of evidence as insufficient (Table 17).

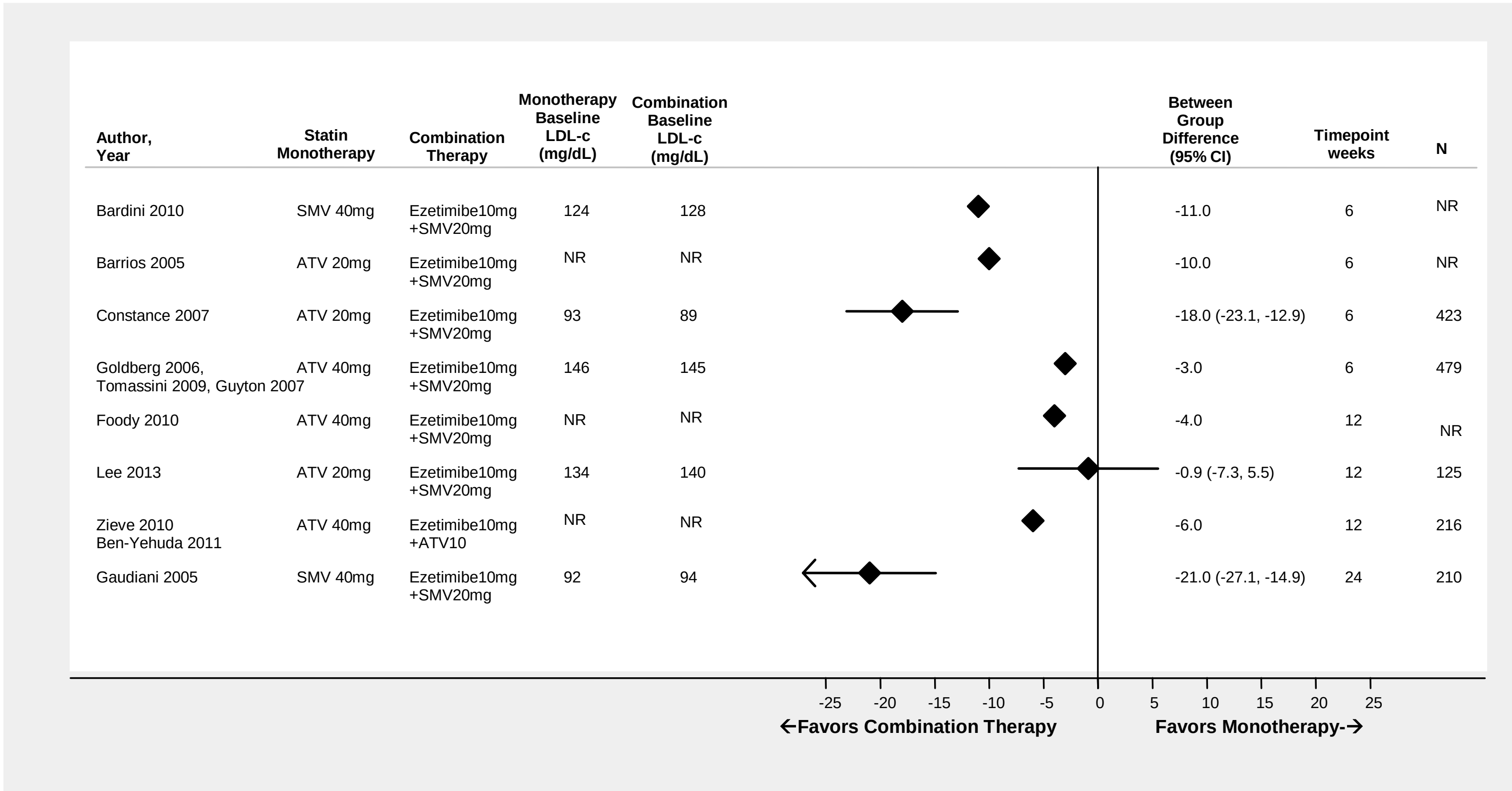
<u>Mid</u> potency statin combination therapy versus <u>high</u> potency statin monotherapy. Eight studies reported LDL-c outcomes among patients with DM.[87-89,97,106,109,124,101,85,98,99] In all studies, combination therapy lowered LDL-c more than monotherapy (difference 2.7% to 20.5%). We graded the strength of evidence as moderate. Although the direction of effect was consistent, the magnitude of effect varied widely, in part due to different doses and different endpoints. Two studies had multiple arms comparing mid potency statin combination therapy with different doses of high potency statin monotherapy.[89,106,101,124] Only the highest dose of statin monotherapy is shown in the Figure 11. Of the other comparison arms, both favored combination therapy (difference 7.6% to 9%). Meta-analysis is not reported due to high heterogeneity (I^2=93.6%).

Three studies reported LDL-c goal attainment (LDL-c <100 mg/dL) among patients with DM.[87-89,106,124] Two studies reported that 2 percent to 37 percent more patients attained this LDL-c goal when taking combination therapy as compared to monotherapy;[88,89] however, the other study reported that 20 percent more patients in the monotherapy arm achieve this LDL-c goal as compared to combination therapy.[87] Another study reported on patients attaining an LDL-c <70 mg/dL among patients with DM.[97] This trial found that 18 percent more patients in the combination arm attained this LDL-c goal as compared to monotherapy.

One study also reported LDL-c outcomes by ethnic subgroups and found similar benefits for black and Hispanic patients with diabetes as those for the general diabetic population.[88] The LS mean percent change comparing combination therapy – monotherapy was -15 percent in black patients and -26 percent in Hispanic patients. [88] Since this is only one trial, the strength of evidence for black patients with diabetes and Hispanic patients with diabetes is still insufficient.

<u>Low</u> potency statin combination therapy versus <u>mid</u> potency statin monotherapy. One study reported LDL-c outcomes among patients with DM.[122] Combination therapy lowered LDL-c 10 percent more than monotherapy. No studies reported LDL-c goal attainment. We graded the strength of evidence as insufficient (Table 19).

Figure 11. Mean difference in percent LDL-c change from baseline to time point comparing mid potency combination therapy with ezetimibe to high potency monotherapy among patients with DM



ATV = atorvastatin; RSV = rosuvastatin; SMV = simvastatin
Note: For diamonds without confidence intervals, SE/SD could not be calculated.

HDL-c

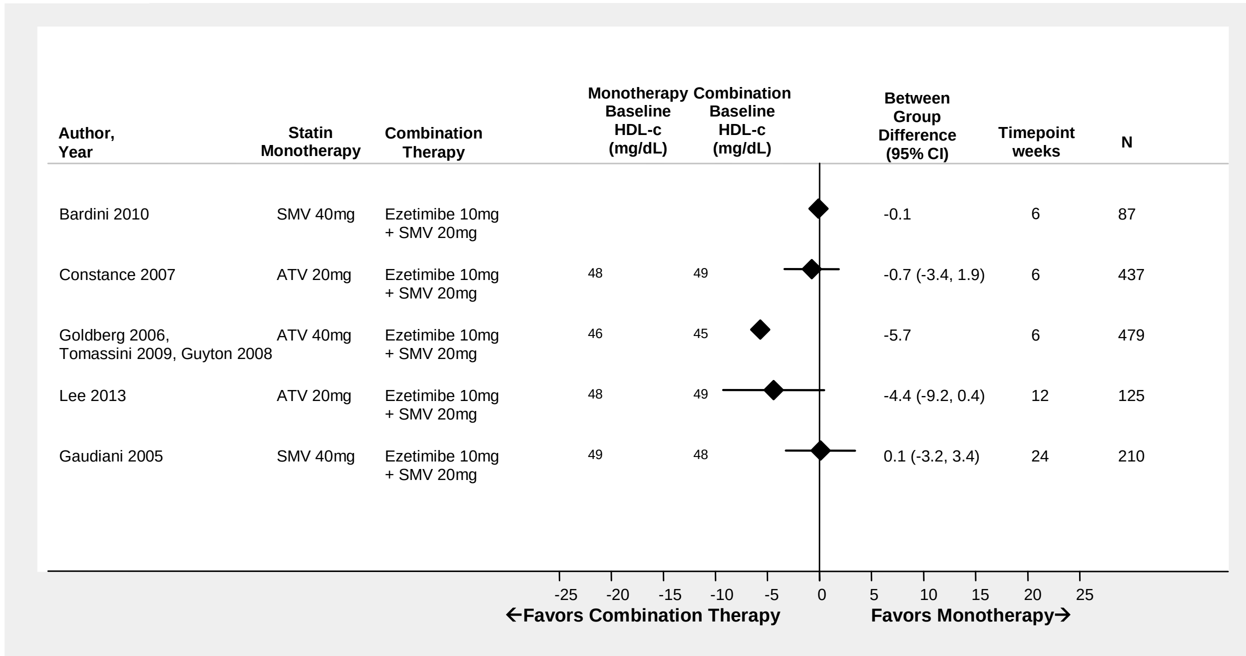
Low potency statin combination therapy versus high potency statin monotherapy. One study reported HDL-c among patients with DM.[79] Combination therapy resulted in no change in HDL-c; however, monotherapy lowered HDL-c by 6 percent. We graded the strength of evidence as insufficient (Table 17).

Mid potency statin combination therapy versus high potency statin monotherapy. Five studies reported HDL-c among patients with DM (8 comparisons).[87-89,101,106,124,97] In three studies, combination therapy increased HDL-c more than monotherapy (difference 1.8% to 5.7%).[88,101] Three studies were neutral (difference 0.1% to 0.74%)[88] Two studies had multiple arms comparing mid potency statin combination therapy with different doses of high potency statin monotherapy.[87,101] Only the highest dose of statin monotherapy is shown in the Figure 12. Of the other comparison arms, two out of two favored combination therapy (difference 3.8% to 4.5%).

We graded the strength of evidence as moderate (Table 18). In meta-analysis, the pooled effect size was -1.02 (95% CI -2.91, 0.86), I^2=15.1% .

Low potency statin combination therapy versus mid potency statin monotherapy. One study reported HDL-c among patients with DM.[122] Combination therapy increased HDL-c by 1 percent more than monotherapy. We graded the strength of evidence as insufficient (Table 19).

Figure 12. Mean difference in percent HDL change from baseline to time point comparing mid potency combination therapy with ezetimibe to high potency monotherapy in patients with DM



ATV = atrovastatin; NR = not reported; SMV = simvastatin
Note: For diamonds without confidence intervals, SE/SD could not be calculated.

Total Cholesterol: HDL-c

Low potency statin combination therapy versus high potency statin monotherapy. No study reported on total cholesterol: HDL-c ratio among patients with DM.

Mid potency statin combination therapy versus high potency statin monotherapy. Two studies reported total cholesterol:HDL ratio among patients with DM.[87,88] Combination therapy lowered total cholesterol: HDL-c by 9.41 percent to 13.5 percent more than monotherapy.

Low potency statin combination therapy versus mid potency statin monotherapy. No study reported on total cholesterol: HDL-c ratio among patients with DM.

Non-HDL-c

Low potency statin combination therapy versus high potency statin monotherapy. No study reported on non-HDL-c among patients with DM.

Mid potency statin combination therapy versus high potency statin monotherapy. Three studies reported on non-HDL-c among patients with DM (4 arms).[87-89,106,124] Three arms favored combination therapy for lowering non-HDL,[88,89] lowering non-HDL by 20 to 47.9 percent (difference 1.7% to 18.3%). One arm favored monotherapy[87], and in that study non-HDL was raised in both groups (raised by 7.43% in the atorvastatin 20 arm and raised by 20.91% in the simvastatin 20/ezetimibe10 arm).

Low potency statin combination therapy versus mid potency statin monotherapy. No study reported on non-HDL-c among patients with DM.

Triglycerides

Low potency statin combination therapy versus high potency statin monotherapy. No study reported on triglycerides among patients with DM.

Mid potency statin combination therapy versus high potency statin monotherapy. Five studies reported on triglycerides among patients with DM (four arms).[87-89,106,124 97,109] Three arms [89 106 87 ,124 ,125] favored monotherapy for triglyceride reduction (difference 2.7% to 4.26%). Two arms favored combination therapy [88 ,97] for triglyceride reduction (difference 4.5% to 6.7%).

Low potency statin combination therapy versus mid potency statin monotherapy. No study reported on triglycerides among patients with DM.

Atherosclerosis

No study reported on measures of atherosclerosis among patients with DM.

Adherence

Low potency statin combination therapy versus high potency statin monotherapy. No study reported on adherence among patients with DM.

Mid potency statin combination therapy versus high potency statin monotherapy. One study reported adherence[87], and showed similar high (98% adherence) adherence between both arms, although the authors did not provide details on how adherence was assessed**.**

Low potency statin combination therapy versus mid potency statin monotherapy. No study reported on adherence among patients with DM.

Musculoskeletal Adverse Events

Low potency statin combination therapy versus high potency statin monotherapy. No study reported on elevations in CPK or cases of myalgia among patients with DM.

Mid potency statin combination therapy versus high potency statin monotherapy. Three studies reported on cases of myalgia among patients with DM.[87,88,109] Events were low and one study favored monotherapy (0.5% in combination therapy patients, 0% in monotherapy patients).[87] One study favored combination therapy (4.8% in monotherapy patients, 1.6% in combination therapy patients) In the third study no events were reported in either arm.[88] One study reported on elevations of CPK > 10 times ULN.[88] Monotherapy was favored.

Low potency statin combination therapy versus mid potency statin monotherapy. No study reported on elevations in CPK or cases of myalgia among patients with DM.

Elevated Liver Transaminases

No study reported on elevations in liver transaminases among patients with DM.

Withdrawal Due to Adverse Events

Low potency statin combination therapy versus high potency statin monotherapy. No study reported on withdrawals due to adverse events among patients with DM.

Mid potency statin combination therapy versus high potency statin monotherapy. Four studies reported withdrawals due to adverse events among patients with DM.[87,88,97,101] Outcomes were low. In two comparisons, there were more withdrawals due to AE in the monotherapy arm than in the combination therapy arm (difference 1.5% to 2.9%)[88,97] In three comparisons, there were more withdrawals in the combination therapy group (difference 0.5% to 2.3%).[88,101]

<u>Low</u> potency statin combination therapy versus <u>mid</u> potency statin monotherapy. No study reported on withdrawals due to adverse events among patients with DM.

Any Adverse Event

<u>Low</u> potency statin combination therapy versus <u>high</u> potency statin monotherapy. No study reported on occurrence of any adverse events among patients with DM.

<u>Mid</u> potency statin combination therapy versus <u>high</u> potency statin monotherapy. Four studies (five comparisons) reported on occurrence of any adverse events among patients with DM.[87,88,97,101] In four comparisons, there were more AEs in the combination therapy group (difference 1.5% to 8.3%). In one comparison, there were more AEs in the monotherapy group (difference 7.5%).

<u>Low</u> potency statin combination therapy versus <u>mid</u> potency statin monotherapy. No study reported on occurrence of any adverse events among patients with DM.

Cancer

No study reported on cancer among patients with DM.

Acute Kidney Injury

No study reported on acute kidney injury among patients with DM.

Elderly Patients (> 75 Years Old)

Two studies reported outcomes for elderly participants.[98,99,101] These trials compared mid potency statin in combination with ezetimibe to high potency statin monotherapy. With respect to clinical outcomes, these studies only reported on mortality and serious adverse events. With respect to surrogate outcomes, they reported on LDL-c, HDL-c, and total cholesterol:HDL ratio. With respect to short-term harms, these trials reported only on.

Mortality

<u>Mid</u> potency statin combination therapy versus <u>high</u> potency statin monotherapy. No deaths occurred in the one study that examined this outcome among elderly patients.[98,99] We graded the strength of evidence as insufficient

Serious Adverse Events

<u>Mid</u> potency statin combination therapy versus <u>high</u> potency statin monotherapy. One study reported on serious adverse events among elderly patients.[98,99] This study reported that 3 percent of elderly patients in the combination arm had a serious adverse event, while no elderly patients in the monotherapy group experienced a serious adverse event. We graded the strength of evidence as insufficient.

LDL-c

<u>Mid</u> potency statin combination therapy versus <u>high</u> potency statin monotherapy. Two studies reported on LDL-c outcomes among elderly patients.[98,99,101]

The LS mean percent change in LDL-c was 14 percent among the elderly participants in the monotherapy arm vs. 28.4 percent among the elderly participants in the combination therapy arm at 6 weeks ($p<0.05$); the LS mean percent change in LDL-c was -20.2 percent in the monotherapy group and -20.6 percent in the combination therapy group at 12 weeks ($p>0.05$).

Another study reported LDL-c change in the elderly subgroup [101] and favored combination therapy for LDL-c change (47.5% decrease in the monotherapy arm compared with 58% decrease in the combination therapy arm).

One study [98,99] examined LDL-c goal attainment in elderly patients, and reported that 45 percent of elderly patients in the combination therapy arm and 56 percent of patients in the monotherapy arm attained LDL-c goals at 12 weeks. We graded the strength of evidence as insufficient.

HDL-c

<u>Mid</u> potency statin combination therapy versus <u>high</u> potency statin monotherapy. One study examined HDL-c among elderly patients.[98,99] This study favored combination therapy at 6 weeks (0.6% HDL-c increase in monotherapy group at 6 weeks, 3.6% HDL-c increase in monotherapy group at 6 weeks) and at 12 weeks (1.4% HDL-c decrease in monotherapy group at 12 weeks, 2.4% HDL-c increase in combination therapy group at 12 weeks). We graded the strength of evidence as insufficient.

Total Cholesterol: HDL

<u>Mid</u> potency statin combination therapy versus <u>high</u> potency statin monotherapy. One study examined total cholesterol: HDL-c change in elderly patients.[98,99] Combination therapy was favored, with a 7.8 percent decrease in total cholesterol:HDL in monotherapy arm participants at 6 weeks, a 19 percent decrease in combination therapy arm participants at 6 weeks; a 10.8 percent decrease in monotherapy participants at 12 weeks and a 14.2 percent decrease in combination therapy patients at 12 weeks.

Any Adverse Event

<u>Mid</u> potency statin combination therapy versus <u>high</u> potency statin monotherapy. One study [98,99] reported adverse events in elderly patients. 31 percent of elderly participants in the monotherapy arm had an AE by 12 weeks, while 30 percent in the combination arm had an AE by 12 weeks.

Withdrawal AE

<u>Mid</u> potency statin combination therapy versus <u>high</u> potency statin monotherapy. One study [98,99] reported withdrawal due to adverse events in elderly patients. 2 percent of elderly participants in the monotherapy arm withdrew due to AE by 12 weeks, while 6 percent in the combination arm withdrew due to AE by 12 weeks.

Elevated Liver Transaminases

Mid potency statin combination therapy versus high potency statin monotherapy. One study examined elevated liver transaminases in elderly patients, which was 0 percent in both groups at 12 weeks.[98,99]

Musculoskeletal Adverse Events

Mid potency statin combination therapy versus high potency statin monotherapy. One study [98,99] examined elevated CPK > 10x ULN in elderly patients, which was 0 percent in both groups at 12 weeks.

Female Patients

Two studies reported outcomes for female participants.[98,99,101] Both trials compared a mid potency statin in combination with ezetimibe to high potency statin monotherapy. These trials only reported on LDL-c outcomes.

LDL-c

Mid potency statin combination therapy versus high potency statin monotherapy. Three studies reported LDL-c outcome among female participants.[88,98,99,101] Combination therapy lowered LDL-c more than monotherapy (difference 8 percent to 18 percent). We graded the strength of evidence as insufficient.

Asian Patients

One study reported outcomes for Asian participants.[101] This trial compared a mid potency statin in combination with ezetimibe to high potency statin monotherapy. This trial only reported on LDL-c outcomes.

LDL-c

Mid potency statin combination therapy versus high potency statin monotherapy. The one study that reported on LDL-c among Asian participants reported that monotherapy decreased LDL-c by 8 percent more than combination therapy. We graded the strength of evidence as insufficient.

Black Patients

One study reported outcomes for black participants.[101] This trial compared a mid potency statin in combination with ezetimibe to high potency statin monotherapy. This trial only reported on LDL-c outcomes.

LDL-c

Mid potency statin combination therapy versus high potency statin monotherapy. Two studies[88,101] reported on LDL-c among black participants. Combination therapy decreased LDL-c by 15 to 16 percent more than monotherapy. We graded the strength of evidence as insufficient.

Hispanic Patients

One study reported outcomes for Hispanic participants.[101] This trial compared a mid potency statin in combination with ezetimibe to high potency statin monotherapy. This trial only reported on LDL-c outcomes.

LDL-c

Mid potency statin combination therapy versus high potency statin monotherapy. One study[88] reported on LDL-c among Hispanic participants. Combination therapy decreased LDL-c by 26 percent more than monotherapy. We graded the strength of evidence as insufficient.

Table 11. Low potency statin in combination with ezetimibe as compared to high potency statin monotherapy in general populations: strength of evidence

Outcome	No. Studies (N)	Risk of Bias	Directness	Consistency	Precision	Reporting Bias Other Issues	Findings and Magnitude of Effect	Strength of Evidence
Long-Term Benefits and Serious Adverse Events								
Mortality	2[a]	Low	NA	Consistent	Imprecise	Not detected None	No deaths in any arm	Insufficient
Acute Coronary Events	None	NA	NA	NA	NA	NA	No eligible studies	Insufficient
Revascularization Procedures	None	NA	NA	NA	NA	NA	No eligible studies	Insufficient
Serious Adverse Events	None	NA	NA	NA	NA	NA	No eligible studies	Insufficient
Surrogate Clinical Outcomes								
LDL-c	13[a] (2392)	Moderate	Indirect [LDL not directly measured in all trials]	Inconsistent [six favored combination, three neutral, three monotherapy]	Imprecise	Not detected None	Six comparisons favored combination therapy for lowering LDL-c as compared to monotherapy (difference 2 percent to 12 percent), three favored monotherapy, four showed no difference.	Low
HDL-c	11 (2128)	Moderate	Direct [HDL directly measured]	Inconsistent [three favored combination, six neutral, one monotherapy]]	Imprecise	Not detected None	Three comparisons favored combination therapy for raising HDL-c as compared to monotherapy (difference5.14 percent to 6.3 percent).	Low

HDL = high-density lipoprotein; LDL = low-density lipoprotein; NA = not applicable
[a]Missing N in at least one trial.

Table 12. Mid potency statin in combination with ezetimibe as compared to high potency statin monotherapy in general populations: strength of evidence

Outcome	No. Studies (N)	Risk of Bias	Directness	Consistency	Precision	Reporting Bias Other Issues	Findings and Magnitude of Effect	Strength of Evidence
Long-Term Benefits and Serious Adverse Events								
Mortality	6[a] (1565)	Low	Direct	Inconsistent	Imprecise [does not meet OIS of 4864]	Not detected None	Very few events; similar mortality in combination therapy and monotherapy arms.	Insufficient
Acute Coronary Events	1 (596)	Low	Direct	NA	Imprecise	Not detected None	Only one event occurring in a combination arm.	Insufficient
Revascularization Procedures	None	NA	NA	NA	NA	NA	No eligible studies	Insufficient
Serious Adverse Events	2 (1391)	Low	Direct	Consistent [no statistically significant difference in SAE in any comparison]	Imprecise [does not meet OIS of 1490]	Not detected None	No difference.	Insufficient
Surrogate Clinical Outcomes								
LDL-c	11[a] (6694)	Low	Indirect [LDL calculated not directly measured in most trials]	Consistent [Eight studies favored combination therapy, two were neutral, two favored monotherapy]	Imprecise	Not detected None	Eight comparisons favored combination therapy for lowering LDL-c as compared to monotherapy (difference 3 percent to 14 percent)	Moderate
HDL-c	10[a] (6434)	Low	Direct [HDL directly measured]	Inconsistent [Six studies favored combination therapy, five neutral]	Imprecise	Not detected None	Six comparisons favored combination therapy for raising HDL-c as compared to monotherapy (difference 1.8 percent to 6 percent)	Low

HDL = high-density lipoprotein; LDL = low-density lipoprotein; NA = not applicable
[a]Missing N in at least one trial.

Table 13. Low potency statin in combination with ezetimibe as compared to mid potency statin monotherapy in <u>general populations</u>: strength of evidence

Outcome	No. Studies (N)	Risk of Bias	Directness	Consistency	Precision	Reporting Bias Other Issues	Findings and Magnitude of Effect	Strength of Evidence
Long-Term Benefits and Serious Adverse Events								
Mortality	2[a] (604)	Low	NA	NA [no deaths either arm]	Imprecise	Not detected None	No deaths in included arms.	Insufficient
Acute Coronary Events	None	NA	NA	NA	NA	NA	No eligible studies	Insufficient
Revascularization Procedures	None	NA	NA	NA	NA	NA	No eligible studies	Insufficient
Serious Adverse Events	1 (596)	High	Direct	NA	Imprecise [OIS 640]	NA	There were more SAEs in the combination therapy arm than the monotherapy arm (not statistically significant)	Insufficient
Surrogate Clinical Outcomes								
LDL-c	6[a] (1615)	Low	Indirect [LDL calculated not directly measured in both trials]	Consistent [All trials favor combination therapy]	Imprecise	Not detected None	All comparisons favored combination therapy for lowering LDL-c as compared to monotherapy (difference 3 percent to 11.3 percent).	Moderate
HDL-c	5[a] (1356)	Low	Direct [HDL calculated directly]	Inconsistent [Three trials favored combination therapy, three were neutral]	Imprecise	Not detected None	Three studies favored combination therapy for raising HDL-c as compared to monotherapy (difference 3 percent to 4 percent)	Low

HDL = high-density lipoprotein; LDL = low-density lipoprotein; NA = not applicable
[a]Missing N in at least one trial.

Table 14. Low potency statin in combination with ezetimibe as compared to high potency statin monotherapy among patients with CHD: strength of evidence

Outcome	No. Studies (N)	Risk of Bias	Directness	Consistency	Precision	Reporting Bias Other Issues	Findings and Magnitude of Effect	Strength of Evidence
Long-Term Benefits and Serious Adverse Events								
Mortality	None	NA	NA	NA	NA	NA	No eligible studies	Insufficient
Acute Coronary Events	None	NA	NA	NA	NA	NA	No eligible studies	Insufficient
Revascularization Procedures	None	NA	NA	NA	NA	NA	No eligible studies	Insufficient
Serious Adverse Events	None	NA	NA	NA	NA	NA	No eligible studies	Insufficient
Surrogate Clinical Outcomes								
LDL-c	None	NA	NA	NA	NA	NA	No eligible studies	Insufficient
HDL-c	None	NA	NA	NA	NA	NA	No eligible studies	Insufficient

CHD = coronary heart disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein; NA = not applicable;

Table 15. Mid potency statin in combination with ezetimibe as compared to high potency statin monotherapy among <u>patients with CHD</u>: strength of evidence

Outcome	No. Studies (N)	Risk of Bias	Directness	Consistency	Precision	Reporting Bias Other Issues	Findings and Magnitude of Effect	Strength of Evidence
Long-Term Benefits and Serious Adverse Events								
Mortality	3[a] (539)	Low	Direct	NA	Imprecise	Not detected None	No mortality in any arm.	Insufficient
Acute Coronary Events	1 (49)	High	Direct	NA	Imprecise	Not detected None	Fatal MI in the combination arm.	Insufficient
Revascularization Procedures	None	NA	NA	NA	NA	NA	No eligible studies	Insufficient
Serious Adverse Events	3 (632)	Low	Direct	Inconsistent [2 favored mono, 1 favored combo]	Imprecise [does not meet OIS of 1864]	Not detected None	Two studies favored monotherapy; one favored combination therapy.	Insufficient
Surrogate Clinical Outcomes								
LDL-c	12[a] (1233)	Low	Indirect [LDL calculated not directly measured in all trials]	Consistent [most but not all favored combo]	Imprecise	Not detected None	In nine comparisons, combination therapy lowered LDL more than monotherapy (difference 5 percent to 15 percent)	Moderate
HDL-c	11[a] (1233)	Low	Direct [HDL directly measured]	Inconsistent [Mixed results – most neutral]	Imprecise	Not detected None	Most studies were neutral (difference 0.1 percent to 5.6%, NS)	Low

CHD = coronary heart disease; LDL = low-density lipoprotein; HDL = high-density lipoprotein; NA = not applicable
[a]Missing N in at least one trial.

Table 16. Low potency statin in combination with ezetimibe as compared to mid potency statin monotherapy among patients with CHD: strength of evidence

Outcome	No. Studies (N)	Risk of Bias	Directness	Consistency	Precision	Reporting Bias Other Issues	Findings and Magnitude of Effect	Strength of Evidence
Long-Term Benefits and Serious Adverse Events								
Mortality	None	NA	NA	NA	NA	NA	No eligible studies	Insufficient
Acute Coronary Events	None	NA	NA	NA	NA	NA	No eligible studies	Insufficient
Revascularization Procedures	None	NA	NA	NA	NA	NA	No eligible studies	Insufficient
Serious Adverse Events	None	NA	NA	NA	NA	NA	No eligible studies	Insufficient
Surrogate Clinical Outcomes								
LDL-c	None	NA	NA	NA	NA	NA	No eligible studies	Insufficient
HDL-c	None	NA	NA	NA	NA	NA	No eligible studies	Insufficient

CHD = coronary heart disease; HDL= high-density lipoprotein; LDL = low-density lipoprotein; NA = not applicable

Table 17. Low potency statin in combination with ezetimibe as compared to high potency statin monotherapy among patients with DM: strength of evidence

Outcome	No. Studies (N)	Risk of Bias	Directness	Consistency	Precision	Reporting Bias Other Issues	Findings and Magnitude of Effect	Strength of Evidence
Long-Term Benefits and Serious Adverse Events								
Mortality	None	NA	NA	NA	NA	NA	No eligible studies	Insufficient
Acute Coronary Events	None	NA	NA	NA	NA	NA	No eligible studies	Insufficient
Revascularization Procedures	None	NA	NA	NA	NA	NA	No eligible studies	Insufficient
Serious Adverse Events	None	NA	NA	NA	NA	NA	No eligible studies	Insufficient
Surrogate Clinical Outcomes								
LDL-c	1 (21)	Low	Indirect [LDL calculated]	NA	Imprecise	Not detected None	Monotherapy therapy lowered LDL-c 2 percent more than combination therapy.	Insufficient
HDL-c	1 (21)	Low	Direct [HDL calculated directly]	NA	Imprecise	Not detected None	Combination therapy resulted in no change in HDL-c; however, monotherapy lowered HDL-c by 6 percent.	Insufficient

DM = diabetes mellitus; HDL = high-density lipoprotein; LDL = low-density lipoprotein; NA = not applicable

Table 18. Mid potency statin in combination with ezetimibe as compared to high potency statin monotherapy among patients with DM: strength of evidence

Outcome	No. Studies (N)	Risk of Bias	Directness	Consistency	Precision	Reporting Bias Other Issues	Findings and Magnitude of Effect	Strength of Evidence
Long-Term Benefits and Serious Adverse Events								
Mortality	2 (806)	Low	Direct	Consistent [favored combo]	Imprecise	Not detected None	Two arms favored combination therapy, with 0.4 percent deaths in the monotherapy arm compared with 0 deaths in the combination arm and 0.5 percent deaths in the monotherapy arm compared with 0 deaths in the combination arm.	Insufficient
Acute Coronary Events	None	NA	NA	NA	NA	NA	No eligible studies	Insufficient
Revascularization Procedures	None	NA	NA	NA	NA	NA	No eligible studies	Insufficient
Serious Adverse Events	5 (1641)	Low	Direct	Inconsistent	Precise [meets OIS of 1208]	Not detected None	In four comparisons, there were more SAEs in the combo therapy group (difference 0.02% to 3.9%). In one comparison, there were more SAEs in the monotherapy group (difference 1.8%). One study reported no SAEs in either arm.	Insufficient

Table 18. Mid potency statin in combination with ezetimibe as compared to high potency statin monotherapy among patients with DM: strength of evidence (continued)

Outcome	No. Studies (N)	Risk of Bias	Directness	Consistency	Precision	Reporting Bias Other Issues	Findings and Magnitude of Effect	Strength of Evidence
Surrogate Clinical Outcomes								
LDL-c	8[a] (1807)	Low [< 1/2 trials low quality]	Indirect [LDL not directly measured in all trials]	Consistent [All trials favor high potency statin monotherapy]	Precise	Not detected None	In all studies, combination therapy lowered LDL more than monotherapy (difference 2.7 percent to 20.5 percent).	Moderate
HDL-c	5 (1578)	Low	Direct [HDL calculated directly]	Consistent [favor mono therapy or neutral]	Imprecise	Not detected None	In three studies, combination therapy increased HDL-c more than monotherapy (difference 1.8 percent to 5.7 percent)	Moderate

DM = diabetes mellitus; HDL= high-density lipoprotein; LDL = low-density lipoprotein; NA = not applicable
[a]Missing N in at least one trial.

Table 19. Low potency statin in combination with ezetimibe as compared to mid potency statin monotherapy among <u>patients with DM</u>: strength of evidence

Outcome	No. Studies (N)	Risk of Bias	Directness	Consistency	Precision	Reporting Bias Other Issues	Findings and Magnitude of Effect	Strength of Evidence
Long-Term Benefits and Serious Adverse Events								
Mortality	None	NA	NA	NA	NA	NA	No eligible studies	Insufficient
Acute Coronary Events	None	NA	NA	NA	NA	NA	No eligible studies	Insufficient
Revascularization Procedures	None	NA	NA	NA	NA	NA	No eligible studies	Insufficient
Serious Adverse Events	None	NA	NA	NA	NA	NA	No eligible studies	Insufficient
Surrogate Clinical Outcomes								
LDL-c	1 (24)	High	NR [not recorded if LDL was measured or calculated]	NA	Imprecise	Not detected None	Combination therapy lowered LDL-c 10% more than monotherapy.	Insufficient
HDL-c	1 (24)	Low	Direct [HDL calculated directly]	NA	Imprecise	Not detected None	Combination therapy increased HDL-c by 1% more than monotherapy.	Insufficient

DM = diabetes mellitus; HDL = high-density lipoprotein; LDL = low-density lipoprotein; NA = not applicable

Combined Lipid-Modifying Therapy With Statin and Fibrate Versus Intensification of Statin Monotherapy

Study Characteristics

We included 4 RCTs (1,341 participants in eligible arms) that compared fibrate plus statin to intensification of statin monotherapy.[70,110,111,123] All trials were parallel arm RCTs. One study was a multicenter trials conducted in North America.[110] Two studies occurred in Europe, one was multicenter[123] and the other single center.[70] The final study was a single center trial in Asia.[111] The treatment duration ranged from 12 to 52 weeks. Two trials included general populations of patients with hyperlipidemia.[70,110] One study included only patients with recent ACS requiring percutaneous inventions, which was one of our subgroups of interest.[111] Another study included only patients with type 2 diabetes with no known coronary artery disease, which was also one of our subgroups of interest.[123] Three trials compared high potency statin monotherapy to mid potency statin in combination therapy.[70,110,111] One trial also allowed comparisons of high potency statin monotherapy to low potency statin in combination with fibrate.[70] One study compared mid potency statin monotherapy to low potency statin in combination therapy among patients with diabetes[123] (Appendix E Evidence Tables).

Population Characteristics

The average participant was in their 50s for all trials. The proportion of female participants varied across trials, ranging from 4 percent to 55 percent. Race, smoking status, prior cardiovascular disease, revascularization events, and diabetes were not consistently reported across trials (Appendix E Evidence Tables).

Interventions

Two trials compared mid potency statin in combination with fibrates to high potency statin monotherapy in general populations.[70,110] Both used simvastatin. One study compared low potency statin in combination with fibrates to high potency statin monotherapy, and used pravastatin.[70] One study compared mid potency statin in combination with fibrates to high potency statin among patients with preexisting CHD, and used atorvastatin and simvastatin.[111] One study compared low potency statin in combination with fibrates to mid potency statin monotherapy among diabetics,[123] and used simvastatin. The trials used fenofibric acid, fenofibrate, gemfibrozil, or ciprofibrate in the combination arms.

Outcomes

Key Points

- **Long-Term Benefits**
  - Insufficient evidence for all potency comparisons.
- **Serious Adverse Events**
  - Insufficient evidence for all potency comparisons.
- **Surrogate Outcomes**
  - There is insufficient evidence to evaluate LDL-c or HDL-c effects of any statin potency.

- **Short-Term Side Effects**
    - Insufficient evidence for all potency comparisons.
- **Adherence**
    - Insufficient evidence for all potency comparisons.
- **Subgroups**
    - Insufficient evidence for all potency comparisons.

Long-Term Benefits and Serious Adverse Events (KQ1)

No studies reported on the comparative effectiveness of fibrate plus statin on long-term benefits as compared to intensification of statin monotherapy among adults regardless of statin potency. We graded the strength of evidence for mortality, acute coronary events, revascularization procedures, and serious adverse events as insufficient.

Surrogate Outcomes, Short-Term Side Effects and Adherence (KQ2)

All included RCTs evaluated surrogate outcomes including LDL -c and HDL-c. In a few RCTs, LDL-c goal attainment, total cholesterol:HDL ratio, medication adherence and adverse events including withdrawal, elevated liver transaminases elevated creatinine phosphokinase, rhabdomyolysis, myalgia, and new diagnosis of acute kidney injury were evaluated. We identified no studies that compared low potency statin in combination with fibrate to mid potency statin monotherapy. We identified no eligible non-randomized extensions of RCTs or FDA reports.

LDL-c

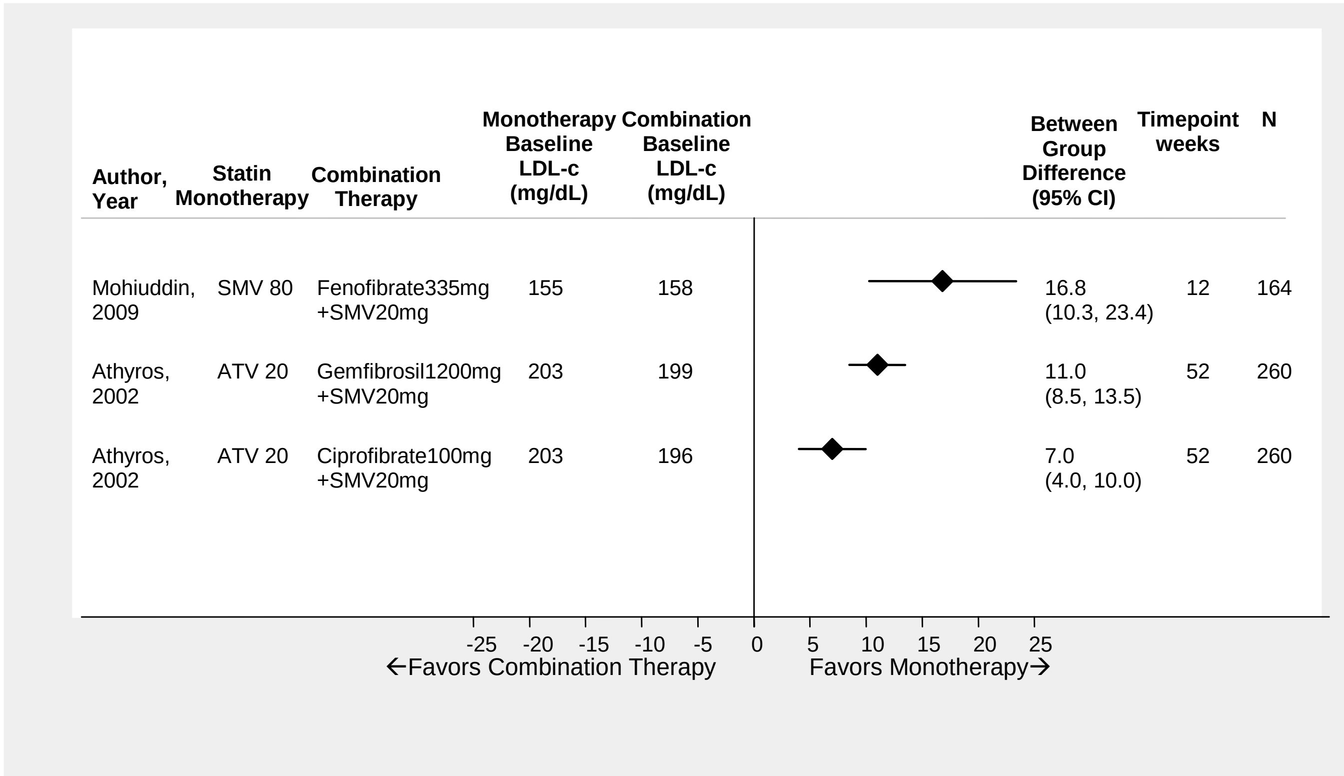
Low Potency Statin Combination Therapy Versus High Potency Statin Monotherapy

One trial reported mean percent change in LDL-c.[70] At 12 months, monotherapy lowered LDL-c 6 percent and 11 percent more than the two combination arms. This trial also reported LDL-c goal attainment, which similarly favored monotherapy (32 percent and 45 percent more patients in monotherapy arm). We graded the strength of evidence as insufficient. (Table 20).

Mid Potency Statin Combination Therapy Versus High Potency Statin Monotherapy

Overall, two trials reported mean percent change in LDL-c.[70,110,127] Monotherapy lowered LDL-c 7 percent to 17 percent more than combination therapy.[70,110] These differences were statistically significant in both trials. Duration of these trials ranged from 12 weeks to 12 months. One trial also reported the proportion of patients achieving LDL-c target and favored monotherapy.[70] The results of all comparisons favored high potency statin monotherapy for lowering LDL-c (Figure 13). We graded the strength of evidence as insuffienct given the paucity of studies (Table 21).

Figure 13. Mean difference in percent LDL change from baseline to time point comparing mid potency combination therapy with fibrates to high potency statin monotherapy



ATV = atorvastatin; NR = not reported; RSV = rosuvastatin; SMV = simvastatin
Note: For diamonds without confidence intervals, SE/SD could not be calculated.

HDL-c

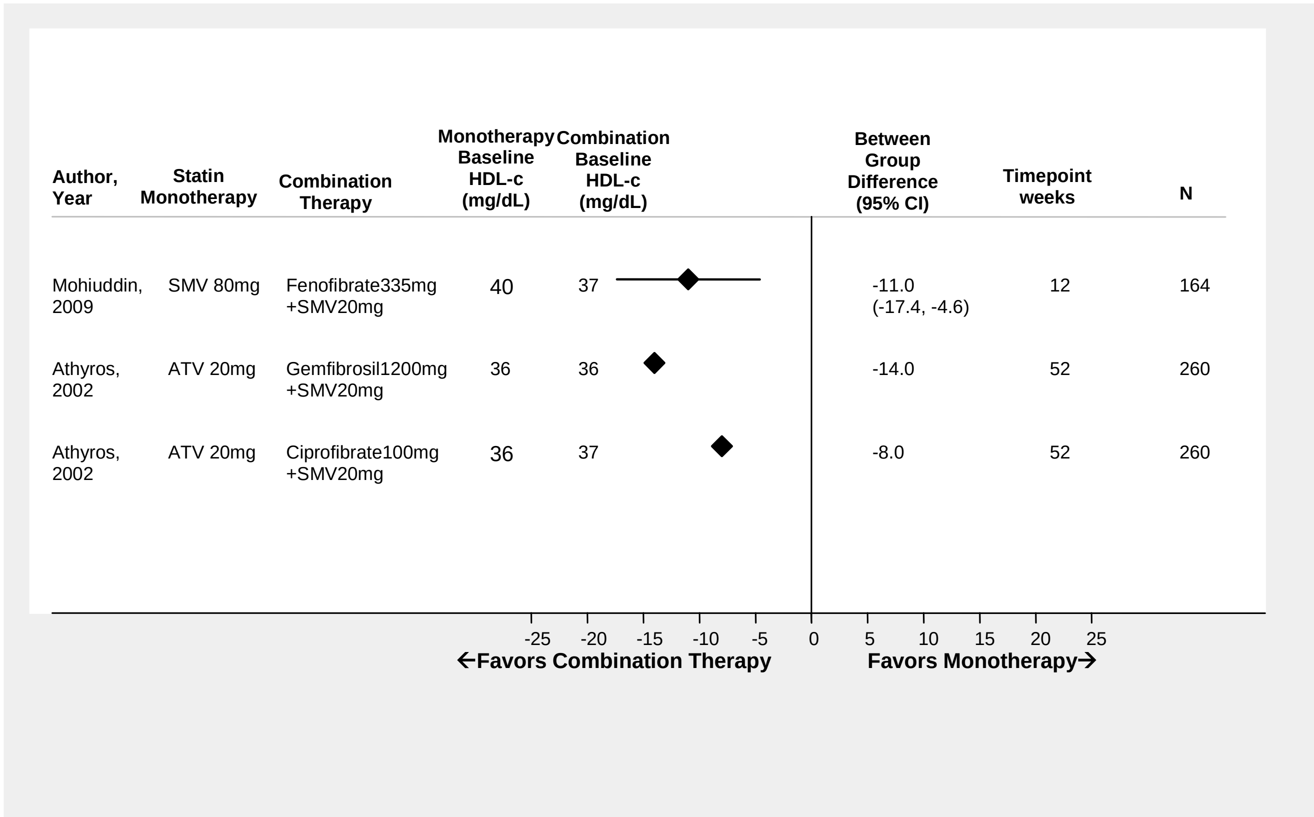
Low Potency Statin Combination Therapy Versus High Potency Statin Monotherapy

One trial reported mean percent change in HDL-c.[70] At 12 months, combination therapy was more effective at increasing HDL-c than monotherapy (difference 9% and 11% favoring combination therapy arms). We graded the strength of evidence as insufficient (Table 20).

Mid Potency Statin Combination Therapy Versus High Potency Statin Monotherapy

Two trials reported mean percent change in HDL-c. [70,110] Combination therapy raised HDL-c 8 percent to 14 percent more than monotherapy (Figure 14). Duration of trials ranged from 12 weeks to 12 months. We graded the strength of evidence as insufficient (Table 21).

Figure 14. Mean difference in percent HDL change from baseline to time point comparing mid potency combination therapy with fibrates to high potency statin monotherapy



ATV = atorvastatin; NR = not reported; RSV = rosuvastatin; SMV = simvastatin
Note: For diamonds without confidence intervals, SE/SD could not be calculated.

Total Cholesterol:HDL Ratio

<u>Low</u> Potency Statin Combination Therapy Versus <u>High</u> Potency Statin Monotherapy

One trial reported mean percent change in total cholesterol:HDL ratio.[70] The monotherapy arm decresed total cholesterol:HDL by 0 percent to 4 percent more than combination therapy. There was no statistically significant between group differences.

<u>Mid</u> Potency Statin Combination Therapy Versus <u>High</u> Potency Statin Monotherapy

One trial reported mean percent change in total cholesterol:HDL ratio.[70] Combination significantly lowered total cholesterol:HDL by 2 percent more than monotherapy at 12 months, which was a statistically significant difference.[70]

Adherence

No studies reported on adherence.

Any Adverse Events

No studies reported on occurrence of at least one adverse event.

Withdrawal Due to Adverse Events

No studies reported on withdrawals due to an adverse event.

Cancer

No studies reported on cancer.

Elevated Liver Transaminases

<u>Low</u> Potency Statin Combination Therapy Versus <u>High</u> Potency Statin Monotherapy

One trial reported on elevated liver transaminases (AST and/or ALT greater than 3 times ULN).[70] At 12 months, no cases of elevated liver transaminases were found in the monotherapy arm, while 1 case found in a combination arm.[70]

<u>Mid</u> Potency Statin Combination Therapy Versus <u>High</u> Potency Statin Monotherapy

Two trials reported on elevated liver transaminases (AST and/or ALT greater than 3 times ULN).[70,110] Overall, few cases of elevated liver transaminases occurred. One trial had one case in the monotherapy arm, while none were reported in the combination arm.[110] At 12 months, the other trial reported no cases of elevated liver transaminases in the monotherapy arm, while 3 cases were found in each of the two combination therapy arms.[70]

Musculoskeletal Adverse Events

<u>Low</u> Potency Statin Combination Therapy Versus <u>High</u> Potency Statin Monotherapy

One trial reported on elevations of CPK greater than 3 times the upper limit of normal.[70] At 12 months, there were no reported cases in the monotherapy arm and one case was identified in one of low potency statin in combination therapy arms.

<u>Mid</u> Potency Statin Combination Therapy Versus <u>High</u> Potency Statin Monotherapy

One trial reported on elevations of CPK greater than 10 times the upper limit of normal. [110] At 12 weeks, there were 2 cases in the combination arm and none in monotherapy arm. Another trial reported elevationsof CPK greater than 3 times the upper limit of normal. There were no cases in the monotherapy arm and 1 case in one of two combination therapy arms at 12 months.[70]

One trial reported on occurrences of myalgia.[110] In this trial, 5 percent of participants had myalgia in the both monotherapy arms and 4 percent of participants had mylagia in the combination arm.[110] This study also reported on the occurrence of rhabdomyolysis, of which there were no cases identified in either arm during follow up.[110]

New Onset Diabetes Mellitus

No studies reported on new onset diabetes.

Acute Kidney Injury

<u>Low</u> Potency Statin Combination Therapy Versus <u>High</u> Potency Statin Monotherapy

No studies reported on acute kidney injury for this comparison.

<u>Mid</u> Potency Statin Combination Therapy Versus <u>High</u> Potency Statin Monotherapy

One trial reported on the occurrence of elevated creatinine.[110] No cases occurred in the monotherapy arms and 4 cases occurred in the combination therapy arm (3.4%).

Subgroups of Patients (KQ 3)

We identified two trials that occurred exclusively among two of our a priori defined subgroups of interest: patients with preexisting CHD[111] and patients with diabetes mellitus.[123]

Patients With Preexisting Coronary Heart Disease

One parallel arm RCT (102 eligible participants) compared high potency statin to mid potency statin in combination with fibrate among patients with preexisting CHD.[111] The study did not report on the comparative effectiveness of fibrate plus statin on long-term benefits as compared to intensification of statin monotherapy for clinical outcomes including mortality, acute coronary events, and revascularization procedures, nor serious adverse events. Given the paucity of studies, we graded the strength of evidence for all outcomes as insufficient (Table 22).

LDL-c

<u>Mid</u> potency statin combination therapy versus <u>high</u> potency statin monotherapy. One trial reported on mean percent change in LDL-c among patients with preexisting CHD.[111] Monotherapy lowered LDL-c by 1 percent to 14 percent more than combination therapy. We graded the strength of evidence as insufficient.

HDL-c

<u>Mid</u> potency statin combination therapy versus <u>high</u> potency statin monotherapy. One trial reported on mean percent change in HDL-c among patients with preexisting CHD.[111] Combination therapy with atorvastatin raised HDL-c by 4 percent to 24 percent more than cmonotherapy. Combination therapy with simvastatin raised HDL-c 16 percent more than atorvastatin monotherapy; however, simvastatin monotherapy produced a 3 percent greater increase in HDL-c as compared to this combination. We graded the strength of evidence as insufficient.

Total Cholesterol: HDL-c Ratio

Mid potency statin combination therapy versus high potency statin monotherapy. One trial reported on mean percent change in total cholesterol:HDL-c ratio among patients with preexisting CHD.[111] At 12 weeks, total cholesterol:HDL-c decreased by 14 percent in the atorvastatin monotherapy arm and by 17 percent in simvastatin monotherapy arm. In the two combination therapy arms, total cholesterol:HDL-c decreased by 23 percent (combination with mid potency atorvastatin) and 16 percent (combination with mid potency simvastatin).[111]

Elevated Liver Transaminases

Mid potency statin combination therapy versus high potency statin monotherapy. One trial reported on occurrence of elevated liver transaminases among patients with preexisting CHD.[111] At 12 weeks, there was no significant elevations of AST and/or ALT greater than 3 times the upper limit of normal found in any arm.

Adverse Musculoskeletal Events

Mid potency statin combination therapy versus high potency statin monotherapy. One trial reported on myalgia among patients with preexisting CHD.[111] At 12 weeks, there were no reported cases on myalgia in the atorvastatin monotherapy arm and 2 cases in simvastatin monotherapy arm. There were no cases in either mid potency statin combination therapy arms.

Patients With Diabetes Mellitus

One parallel arm RCT (291 eligible participants) compared mid potency statin to low potency statin in combination with fibrate.[123] The study did not report on the comparative effectiveness of fibrate plus statin on long-term benefits as compared to intensification of statin monotherapy for mortality or revascularization procedures. Given the paucity of studies, we graded the strength of evidence for all outcomes as insufficient (Table 23).

Acute Coronary Events

Low potency statin combination therapy versus mid potency statin monotherapy. One trial reported on acute coronary events among patients with DM.[123] At 24 weeks, no cases of MI occured in the monotherapy arm and one MI occured in combination therapy arm.

Cerebrovascular Disease

Low potency statin combination therapy versus mid potency statin monotherapy. One trial reported on cerebrovascular events among patients with DM.[123] At 24 weeks, one TIA occurred in the monotherapy arm and no events in the combination therapy arm.

Serious Adverse Events

<u>Low</u> potency statin combination therapy versus <u>mid</u> potency statin monotherapy. One trial reported on serious adverse events among patients with DM.[123] At 24 weeks, one serious adverse event in each arm (1% of patients).

LDL-c

<u>Low</u> potency statin combination therapy versus <u>mid</u> potency statin monotherapy. One trial reported the mean percent LDL-c change among patients with DM.[123] Monotherapy decreased LDL-c 2 percent more than combination therapy, which was not a significant between group differences. This trial also reported proporiton of patient that achieve an LDL-c <100 mg/dL. Interestingly, 6 percent more patients in the combination arm attained this LDL-c goal as compared to the monotherapy group at 12 weeks followup.

HDL-c

<u>Low</u> potency statin combination therapy versus <u>mid</u> potency statin monotherapy. One trial reported the mean percent HDL-c change among patients with DM.[123] Combination therapy significantly raised HDL-c 4 percent more than the monotherapy arm.

Non-HDL-c

<u>Low</u> potency statin combination therapy versus <u>mid</u> potency statin monotherapy. One trial reported the mean percent non-HDL-c change among patients with DM.[123] Combination therapy decreased non-HDL-c 6 percent more than monotherapy.

Triglycerides

<u>Low</u> potency statin combination therapy versus <u>mid</u> potency statin monotherapy. One trial reported the mean percent change in triglycerides among patients with DM.[123] Combination therapy lowered triglycerides 31 percent more than monotherapy at 12 weeks.

Adherence

<u>Low</u> potency statin combination therapy versus <u>mid</u> potency statin monotherapy. One trial reported on adherence among patients with DM.[123] At 12 weeks, the trial reported 98 percent treatment adherence in the mid potency statin monotherapy arm and 99 percent treatment adherence in the low potency statin combination arm. In this trial, adherence to medication was defined >80 percent compliance.[123]

Any Adverse Event

<u>Low</u> potency statin combination therapy versus <u>mid</u> potency statin monotherapy. One trial reported the occurrence of at least one adverse event among patients with DM.[123] At 12 weeks, the trial reported 15 percent of participants in the monotherapy arm and 17 percent in the combination therapy arm had at least one adverse event.

Musculoskeletal Adverse Events

<u>Low</u> potency statin combination therapy versus <u>mid</u> potency statin monotherapy. One trial reported on the occurrence of CPK elevations among patients with DM.[123] There were no cases of CPK elevations >10 times ULN in either arm.

Acute Kidney Injury

<u>Low</u> potency statin combination therapy versus <u>mid</u> potency statin monotherapy. One trial reported the occurrence of acute kidney injury among patients with DM.[123] There were no cases in either arm.

Table 20. Low potency statin in combination with fibrate as compared to high potency statin monotherapy in general populations: strength of evidence domains and summary of key findings

Outcome	No. Studies (N)	Risk of Bias	Directness	Consistency	Precision	Reporting Bias Other Issues	Findings and Magnitude of Effect	Strength of Evidence
Long-Term Benefits and Serious Adverse Events								
Mortality	None	NA	NA	NA	NA	NA NA	No eligible studies	Insufficient
Acute Coronary Events	None	NA	NA	NA	NA	NA NA	No eligible studies	Insufficient
Revascularization Procedures	None	NA	NA	NA	NA	NA NA	No eligible studies	Insufficient
Serious Adverse Events	None	NA	NA	NA	NA	NA NA	No eligible studies	Insufficient
Surrogate Clinical Outcomes								
LDL-c	1 (396)	Low [Jadad score 3]	Indirect [Calculated]	NA	Precise	None detected None	High potency statin monotherapy lowered LDL-c 6-11% more than combination arms at 12 months.	Insufficient
HDL-c	1 (396)	Low [Jadad score 3]	Direct [Measured]	NA	Precise	None detected None	Low potency combination therapy raises HDL-c by 9-11% more than high potency statin monotherapy at 12 months.	Insufficient

NA = not applicable

Table 21. Mid potency statin in combination with fibrate as compared to high potency statin monotherapy in general populations: strength of evidence domains and summary of key findings

Outcome	No. Studies (N)	Risk of Bias	Directness	Consistency	Precision	Reporting Bias Other Issues	Findings and Magnitude of Effect	Strength of Evidence
Long-Term Benefits and Serious Adverse Events								
Mortality	None	NA	NA	NA	NA	NA NA	No eligible studies	Insufficient
Acute Coronary Events	None	NA	NA	NA	NA	NA NA	No eligible studies	Insufficient
Revascularization Procedures	None	NA	NA	NA	NA	NA NA	No eligible studies	Insufficient
Serious Adverse Events	None	NA	NA	NA	NA	NA NA	No eligible studies	Insufficient
Surrogate Clinical Outcomes								
LDL-c	2 (683)	Moderate [Jadad<3 in 1 trial]	Direct	Consistent [Comparisons favor monotherapy]	Precise	None detected None	High potency statin monotherapy lowers LDL-c by 7% to 17% more than combination therapy.	Insufficient
HDL-c	2 (683)	Moderate [Jadad<3 in 1 trial]	Direct	Consistent [Comparisons favor combination therapy]	Precise	None detected None	Combination therapy raises HDL-c 8% to 14% more than high potency statin monotherapy.	Insufficient

NA = not applicable

Table 22. Mid potency statin in combination with fibrate as compared to high potency statin monotherapy among patients with CHD: strength of evidence domains and summary of key findings

Outcome	No. Studies (N)	Risk of Bias	Directness	Consistency	Precision	Reporting Bias Other Issues	Findings and Magnitude of Effect	Strength of Evidence
Long-Term Benefits and Serious Adverse Events								
Mortality	None	N/A	N/A	NA	NA	NA NA	No eligible studies	Insufficient
Acute Coronary Events	None	NA	NA	NA	NA	NA NA	No eligible studies	Insufficient
Revascularization Procedures	None	NA	NA	NA	NA	NA NA	No eligible studies	Insufficient
Serious Adverse Events	None	NA	NA	NA	NA	NA NA	No eligible studies	Insufficient
Surrogate Clinical Outcomes								
LDL-c	1 (102)	High [Jadad<3]	Direct [Measured]	N/A	Imprecise	None detected None	Monotherapy lowered LDL-c by 1% to 14% percent more than combination therapy	Insufficient
HDL-c	1 (102)	High [Jadad<3]	Direct [Measured]	N/A	Imprecise	None detected None	Combination therapy raised HDL-c by 4% to 24% more than atorvastatin monotherapy	Insufficient

CHD = coronary heart disease; NA = not applicable

Table 23. Low potency statin in combination with fibrates as compared to mid potency statin monotherapy among patients with diabetes mellitus: strength of evidence domains and summary of key findings

Outcome	No. Studies (N)	Risk of Bias	Directness	Consistency	Precision	Reporting Bias Other Issues	Findings and Magnitude of Effect	Strength of Evidence
Long-Term Benefits and Serious Adverse Events								
Mortality	1 (291)	Low	Direct	NA	Imprecise	None detected None	No reported deaths in both arms	Insufficient
Acute Coronary Events	1 (291)	Low	Direct	NA	Imprecise	None detected None	No difference between groups	Insufficient
Revascularization Procedures	None	NA	NA	NA	NA	NA NA	No eligible studies	Insufficient
Serious Adverse Events	1 (291)	Low	Direct	NA	Precise	None detected None	No difference between groups	Insufficient
Surrogate Clinical Outcomes								
LDL-c	1 (291)	Low	Direct	N/A	Precise	None detected None	Monotherapy decreased LDL-c 2% more than combination therapy	Insufficient
HDL-c	1 (291)	Low	Direct	N/A	Precise	None detected None	Combination therapy significantly raised HDL-c 4 % more than monotherapy	Insufficient

NA = not applicable

Combined Lipid-Modifying Therapy With Statin and Niacin Versus Intensification of Statin Monotherapy

Study Characteristics

We included five trials (612 participants in eligible arms) that compared niacin plus statin to intensification of statin monotherapy. All trials were parallel arm randomized controlled trials that took place in North America.[81,95,119-121] All trials were multicenter, except for one single center trial.[119] Eligibility criteria were similar across all trials. All trials included a dietary run in, followed by treatment ranging from 6 weeks to 52 weeks in duration. Two trials compared mid potency statin in combination therapy to high potency statin monotherapy.[81,95] The other three trials compared low potency statin in combination therapy to mid potency statin monotherapy[119-121] (Appendix E Evidence Tables).

Population Characteristics

In four trials,[90,95,119-121] the average participant was in their 50s with the mean age ranging from 49-61 years. In the other trial, the study's average participant was in their 70s.[81] Female participants varied between trials and ranged from 21 to 79 percent in each arm. Race was reported in most trials, and the majority of participants were white (range 61 to 96 percent of participants in included arms). The arms in one trial differed significantly by race.[81] Smoking status, prior cardiovascular disease, revascularization events, and diabetes were not consistently reported across trials. When reported, no significant between group differences existed in the trials[95,119,120] (Appendix E Evidence Tables).

Interventions

Two trials compared mid potency statin in combination with extended release niacin to high potency statin monotherapy.[81,95] These monotherapy arms used atorvastatin, and simvastatin, and the combination arms used lovastatin or simvastatin. Three trials compared mid potency statin monotherapy to low potency statin in combination with niacin.[119-121] All these trials used lovastatin as the statin in both the monotherapy and combination therapy arms. Across all trials, patients had their dose of niacin titrated up over the study period with the final doses ranging from 1g to 2.5g.

Outcomes

Key Points

- **Long-Term Benefits**
    - Insufficient evidence for all potency comparisons.
- **Serious Adverse Events**
    - Insufficient evidence for all potency comparisons.
- **Surrogate Outcomes**
    - There is insufficient evidence to compare combined lipid-modifying therapy with niacin and statin to instensificatin of statin monotherapy on lowering LDL-c, regardless of statin potency

- A low potency statin monotherpy with niacin is more effective than mid potency statin monotherapy for raising HDL-c (SOE: moderate). There is insufficient evidence within other potency comparisons.

- **Adherence**
  - Insufficient evidence for all potency comparisons.
- **Short-Term Side Effects**
  - There is insufficient evidence to compare the rates of adverse events for any statin potency comparisons.
  - The evidence suggests that there is no difference in the rates of elevated liver transaminases between combined lipid-modifying therapy with niacin and mid potency statin to high potency statin monotherapy. There is insufficient evidence within other potency comparisons.
  - There is insufficient evidence to compare the rates of adverse musculoskeletal events for any statin potency comparisons.
- **Subgroups**
  - Insufficient evidence for all potency comparisons.

Long-Term Benefits and Serious Adverse Events (KQ 1)

Few studies reported on the comparative effectiveness of niacin plus statin on long-term benefits as compared to intensification of statin monotherapy among adults. We graded the strength of evidence for mortality, acute coronary events, revascularization procedures, and serious adverse events as insufficient (Table 24). We identified no studies that compared low potency statin combination therapy to high potency statin monotherapy.

Mortality

Mid Potency Statin Combination Therapy Versus High Potency Statin Monotherapy

No studies reported deaths.

Low Potency Statin Combination Therapy Versus Mid Potency Statin Monotherapy

One study reported the number of deaths during the trial.[120] There was one death in both the mid potency statin monotherapy arm and the low potency statin combination arm; both were considered vascular deaths.

Acute Coronary Events

Mid Potency Statin Combination Therapy Versus High Potency Statin Monotherapy

One study evaluated counts of ACS events during the 12-month study period.[81] One ACS event occurred in the monotherapy arm, while there were no events in the combination therapy arm. There was no between group difference reported.

Low Potency Statin Combination Therapy Versus Mid Potency Statin Monotherapy

No studies reported on acute coronary events.

Cerebrovascular Disease

No studies reported on cerebrovascular events.

Revascularization Procedures

No studies reported on revascularization procedures.

Serious Adverse Events

No studies reported on serious adverse events.

Surrogate Outcomes, Short-Term Side Effects and Adherence (KQ 2)

All included RCTs evaluated surrogate outcomes including LDL-c and HDL-c. In several RCTs, medication adherence and short-term side effects were evaluated including elevated liver transaminases and elevated creatinine phosphokinase. We identified no studies that compared high potency statin monotherapy to low potency statin combination therapy. We identified no eligible non-randomized extensions of RCTs or FDA reports.

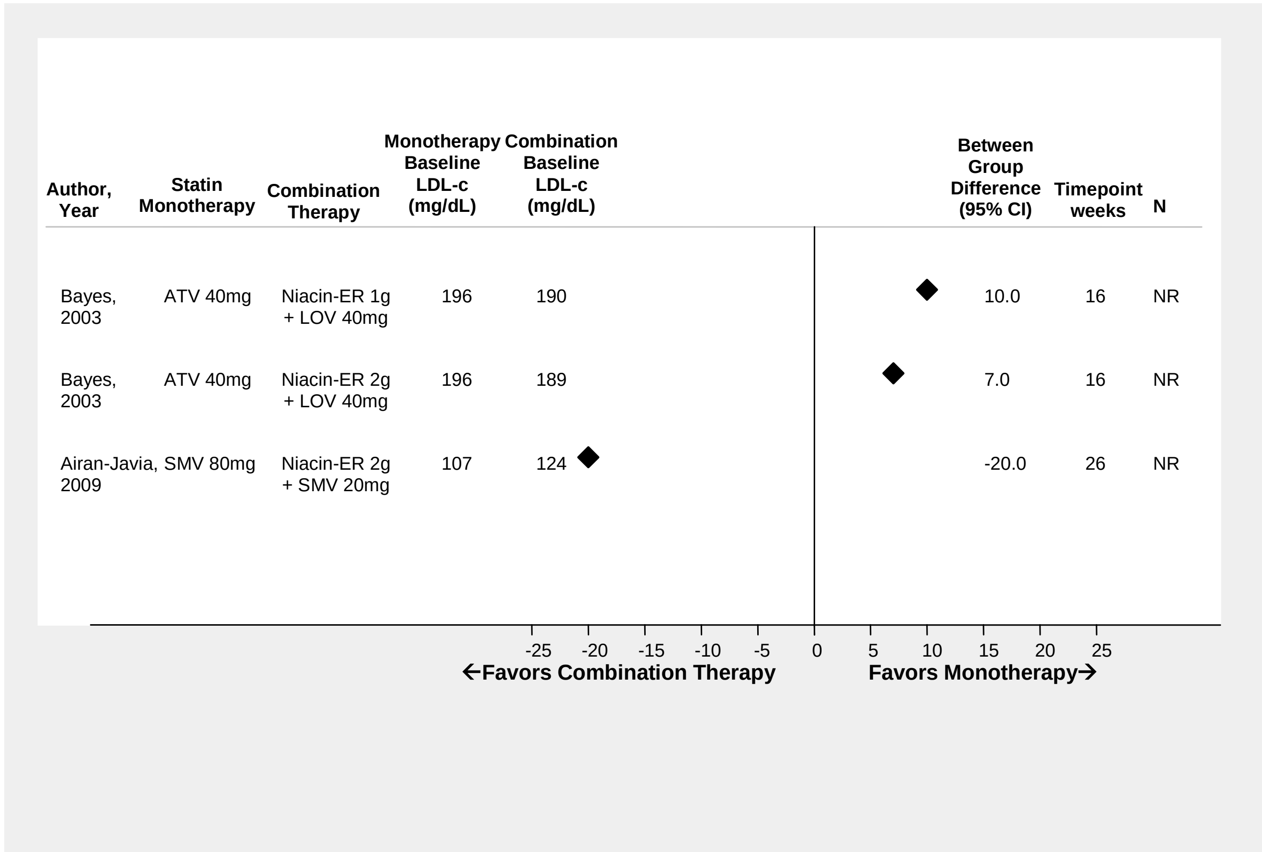
LDL-c

Mid Potency Statin Combination Therapy Versus High Potency Statin Monotherapy

Two trials reported mean percent change in LDL-c (3 comparisons).[81,95] In one trial, one comparison favored monotherapy for lowering LDL-c (1 percent to 12 percent greater decrease) as compared to combination therapy.[95] In one trial, one comparison found no difference between monotherapy and combination therapy for lowering LDL-c.[95] Finally, two comparisons reported in two trials favored combination therapy for lowering LDL-c (3 percent to 22 percent greater decrease) as compared to monotherapy.[81,95]

The results did not favor either high potency statin monotherapy or mid potency statin in combination with niacin for lowering LDL-c (Figure 15). One trial strongly trial favored combination therapy,[81] and differed from the other trial in several ways. First, patients had to have hyperlipidemia and at least 30 percent carotid stenosis on ultrasound to be included, whereas all other trials recruited patients based only on have hyperlipidemia. Second, the baseline LDL values in this trial were much lower than the other trial, as there was no washout of prior lipid-lowering medications. Finally, the baseline LDL value in the monotherapy arm was lower (median 107 mg/dL) than the combination therapy arm (124mg/dL). All three of these factors may explain the different results in this trial. We graded the strength of evidence as insufficient (Table 24).

Figure 15. Mean difference in percent LDL change from baseline to time point comparing mid potency combination therapy with niacin to high potency monotherapy



ATV = atrovastatin; ER = extended release; LOV = Lovastatin; NR = not reported; RSV = rosuvastatin; SMV = simvastatin
Note: For diamonds without confidence intervals, SE/SD could not be calculated.

<u>Low</u> Potency Statin Combination Therapy Versus <u>Mid</u> Potency Statin Monotherapy

Three trials reported mean percent LDL-c change.[119-121] Overall, the effects on LDL-c were variable. At 6 weeks,[119] one trial found that both the statin monotherapy arm and combination arm reduced LDL-c by 8 percent. At 20 weeks,[121] another trial found that the two combination arms each reduced LDL-c 12 percent more than the statin monotherapy arm. At 28 weeks, the final trial found that monotherapy decreased LDL-c 4 percent more than combination therapy.[120]

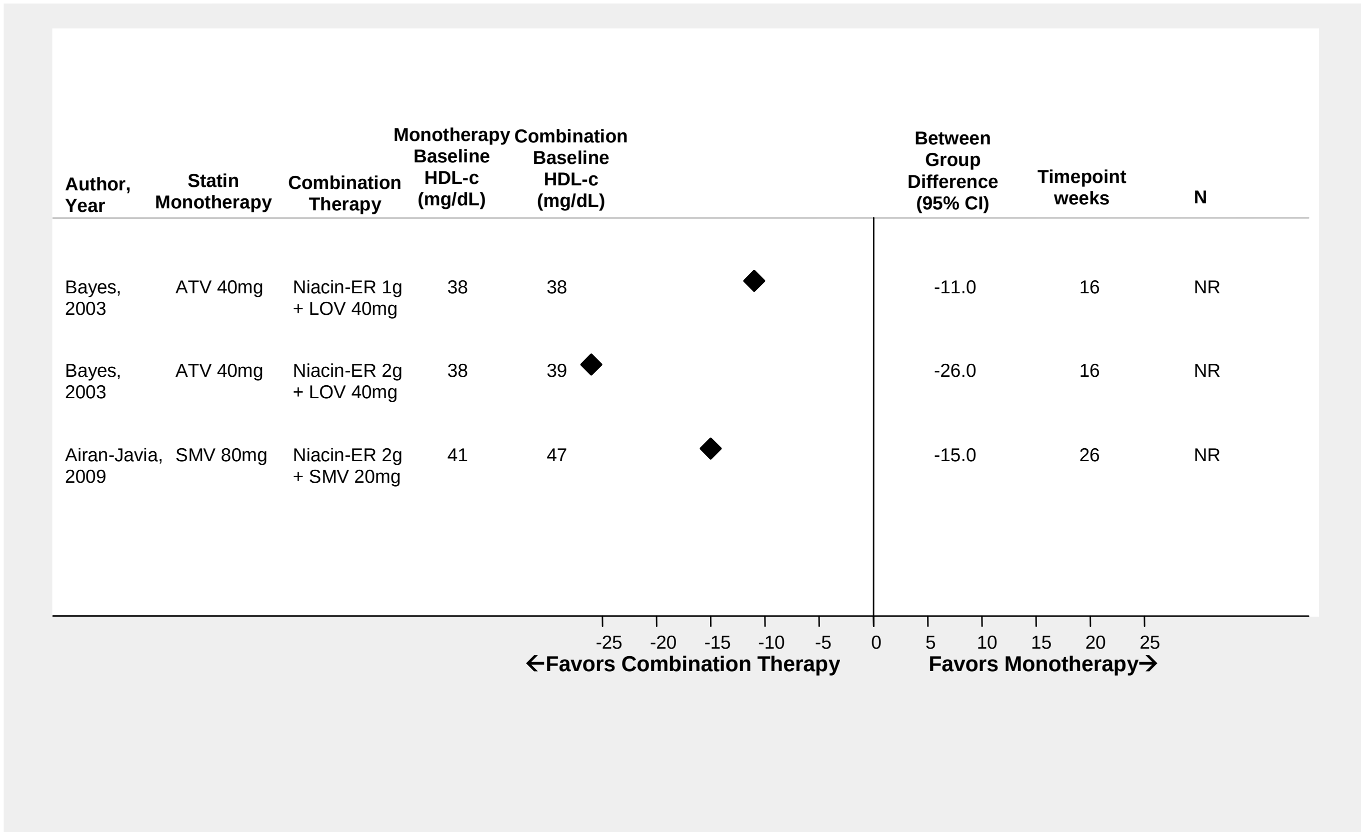
The results did not favor either mid potency statin monotherapy or low potency statin in combination with niacin for lowering LDL-c. In one trial that favored combination therapy,[121] investigators used higher doses of niacin-ER (2.5g) than the other trial that favored statin monotherapy (niacin-ER 1g).[120] This difference in niacin dose may explain the difference in LDL effect among these trials. We graded the strength of evidence as insufficient (Table 25). While three trials reported on this comparison, only one of the trials reported or provided sufficient information for us to calculate SE for the LDL-c difference in differences. Therefore, we did not perform meta-analysis.

HDL-c

<u>Mid</u> Potency Statin Combination Therapy Versus <u>High</u> Potency Statin Monotherapy

Two trials reported mean percent change in HDL-c.[81,95] Both trials favored combination therapy in raising HDL-c (10 percent to 26 percent greater increase) as compared to monotherapy (Figure 16). Treatment duration ranged from 8 weeks to 12 months. We graded the strength of evidence as insufficient, given the paacity of studies.

Figure 16. Mean difference in percent HDL change from baseline to time point comparing mid potency combination therapy with niacin to high potency statin monotherapy



ATV = atrovastatin; ER = extended-release; NR = not reported; RSV = rosuvastatin; SMV = simvastatin
Note: For diamonds without confidence intervals, SE/SD could not be calculated.

<u>Low</u> Potency Statin Combination Therapy Versus <u>Mid</u> Potency Statin Monotherapy

Three trials reported mean percent change in HDL-c.[119-121] All trials favored combination therapy in raising HDL-c (15 percent to 27 percent greater increase) as compared to monotherapy . We graded the strength of evidence as moderate (Table 23). While three trials reported on this comparison, only one of the trials reported or provided sufficient information for us to calculate SE for the HDL-c difference in differences. Therefore, we did not perform meta-analysis.

Total Cholesterol: HDL

No studies reported mean percent change in total cholesterol:HDL ratio.

Atherosclerosis

No studies reported on atherosclerosis.

Adherence

<u>Mid</u> Potency Statin Combination Therapy Versus <u>High</u> Potency Statin Monotherapy

One trial reported on treatment adherence.[95,128] Adherence was ≥94 percent in all arms at 16 weeks.

<u>Low</u> Potency Statin Combination Therapy Versus <u>Mid</u> Potency Statin Monotherapy

One trial reported on treatment adherence.[121] Adherence to medications was 96 percent in both arms at 20 weeks.

Any Adverse Event

<u>Mid</u> Potency Statin Combination Therapy Versus <u>High</u> Potency Statin Monotherapy

No studies reported on the occurrence of at least one adverse event for this comparison.

<u>Low</u> Potency Statin Combination Therapy Versus <u>Mid</u> Potency Statin Monotherapy

One trial reported the number of participants who experienced at least one adverse event.[121] In the statin monotherapy arm, 52 percent of participants had at least one adverse event, while 44 percent in one combination arm (N-ER 2.5g + LOV 10mg) and 62 percent in the other combination arm (N-ER 2.5g + LOV 20mg) had at least one adverse event during the 20-week study period. Calculated p-values for these comparisons were not significant.

Withdrawal Due to Adverse Events

<u>Mid</u> Potency Statin Combination Therapy Versus <u>High</u> Potency Statin Monotherapy

No studies reported withdrawals due to adverse events.

<u>Low</u> Potency Statin Combination Therapy Versus <u>Mid</u> Potency Statin Monotherapy

One trial reported the number of participants who withdrew from the study due to an adverse event.[120] At 28 weeks, 19 percent of participants in the mid potency statin monotherapy arm and 10 percent in the low potency statin combination arm withdrew due to an adverse event, which was not significantly different.

Cancer

No studies reported on cancer.

Elevated Liver Transaminases

Mid Potency Statin Combination Therapy Versus High Potency Statin Monotherapy

Two trials reported on significant elevations in AST and/or ALT.[81,95,128] There were no reported cases of elevated AST and/or ALT greater than 3 times the ULN in one trial.[95,128] The other trial reported that 1 participant experienced liver transaminase elevations in the high potency statin monotherapy arm and no cases in the mid potency statin combination arm.[81]

Low Potency Statin Combination Therapy Versus Mid Potency Statin Monotherapy

Two trials reported on significant elevations in AST and/or ALT.[120,121] There were two cases of elevated AST and/or ALT greater than 3 times the ULN at 20 weeks in one trial, one in each combination arm (N-ER 2.5g + LOV 10mg and N-ER 2.5g + LOV 20mg).[121] While there was one case of elevated AST and/or ALT greater than 3 times the ULN in the statin monotherapy arm at 28 weeks in the other trial.[120]

Adverse Musculoskeletal Events

Mid Potency Statin Combination Therapy Versus High Potency Statin Monotherapy

One trial reported on occurrences of myalgia.[81] There were 2 cases of muscle cramping in the high potency statin monotherapy arm and no cases in the mid potency combination arm.[81]

One trial reported on elevations of CPK.[95] No cases of CPK elevations greater than 5 times the upper limit of normal were identified at 16 weeks.

Low Potency Statin Combination Therapy Versus Mid Potency Statin Monotherapy

One trial reported on occurrences of myalgia.[120] At 28 weeks, 7 percent of participants in the monotherapy arm and 4 percent in the combination arm reported muscle aches.

Two trials reported on elevations of CPK.[120,121] One trial reported on CPK elevations greater than 3 times the ULN at 20 weeks,[121] while the other reported on CPK elevations greater than 10 times the ULN at 28 weeks.[120] No cases of CPK elevations were identified in either trial.

New Onset Diabetes Mellitus

Mid Potency Statin Combination Therapy Versus High Potency Statin Monotherapy

No studies compared any diabetes-related outcomes.

Low Potency Statin Combination Therapy Versus Mid Potency Statin Monotherapy

Two trials reported on hyperglycemia.[120,121] At 20 weeks, there were no cases of hyperglycemia in the statin monotherapy arm, while 6 percent and 3 percent of patients in the combination therapy arms (N-ER 2.5g + LOV 10mg and N-ER 2.5g + LOV 20mg, respectively) experienced hyperglycemia.[121] In the other trial, 7 percent of monotherapy arm participants and 4 percent of combination arm participants had fasting glucose elevated greater than 1.3 times the ULN at 28 weeks.[120]

Acute Kidney Injury

No studies reported on acute kidney injury.

Subgroups of Patients (KQ 3)

No studies reported on the comparative effectiveness of niacin plus statin on benefits or harms as compared to intensification of statin monotherapy among subgroups.

Table 24. Mid potency statin in combination with niacin as compared to high potency statin monotherapy in general populations: strength of evidence domains and key findings

Outcome	No. Studies (N)	Risk of Bias	Directness	Consistency	Precision	Reporting Bias Other Issues	Findings and Magnitude of Effect	Strength of Evidence
Long-Term Benefits and Serious Adverse Events								
Mortality	None	NA	NA	NA	NA	NA NA	No eligible studies	Insufficient
Acute Coronary Events	1 (50)	Low [Double blind; low attrition]	Direct	NA	Imprecise	None detected None	One ACS event in the high potency monotherapy arm and no events in the combination arm at 12 months.	Insufficient
Revascularization Procedures	None	NA	NA	NA	NA	NA NA	No eligible studies	Insufficient
Serious Adverse Events	None	NA	NA	NA	NA	NA NA	No eligible studies	Insufficient
Surrogate Clinical Outcomes								
LDL-c	2 (365)	Moderate [1 trials with Jadad score<3; 1 trial from 2013 update with low risk of bias]	Indirect [LDL calculated in 1 trials]	Inconsistent [2 comparisons favor statin monotherapy; 2 comparisons favors combination therapy; 1 comparison no difference]	Imprecise	None detected None	Inconsistent effects on LDL-c when comparing combination therapy with niacin and statin to intensification of statin monotherapy.	Insufficient
HDL-c	2 (365)	Moderate [1 trials with Jadad score<3; 1 trial from 2013 update with low risk of bias]	Direct [HDL measured in all trials]	Consistent [All comparisons favor combination therapy]	Imprecise	None detected None	All studies favor mid potency combination therapy by raising HDL-c by 10-26% more than high potency statin monotherapy at 8-26 weeks.	Insufficient

HDL = high-density lipoprotein; LDL = low-density lipoprotein; NA = not applicable

Table 25. Low potency statin in combination with niacin as compared to mid potency statin monotherapy in general populations: strength of evidence domains and key findings

Outcome	No. Studies (N)	Risk of Bias	Directness	Consistency	Precision	Reporting Bias Other Issues	Findings and Magnitude of Effect	Strength of Evidence
Long-Term Benefits and Serious Adverse Events								
Mortality	1 (118)	Low [Jadad score≥3]	Direct	NA	Imprecise	None detected None	One death in the mid potency statin monotherapy group and one death in the low potency statin in combination with niacin group at 28 weeks.	Insufficient
Acute Coronary Events	None	NA	NA	NA	NA	NA NA	No eligible studies	Insufficient
Revascularization Procedures	None	NA	NA	NA	NA	NA NA	No eligible studies	Insufficient
Serious Adverse Events	None	NA	NA	NA	NA	NA NA	No eligible studies	Insufficient
Surrogate Clinical Outcomes								
LDL-c	3 (247)	Low [1 trial with Jadad score<3]	Indirect [LDL calculated in 2 trials]	Inconsistent [1 comparison favors monotherapy; 2 comparisons favor combination therapy; 1 comparison with no difference]	Imprecise	None detected None	Three studies show no consistent effect in LDL-c reduction between mid potency statin montherapy and low potency statin in combination with niacin at 6-28 weeks.	Insufficient
HDL-c	3 (247)	Low [1 trial with Jadad score<3]	Direct [HDL measured in all trials]	Consistent [All trials favor combination therapy]	Imprecise	None detected None	All studies favor low potency combination therapy by raising HDL-c by 15-27% more than mid potency statin monotherapy at 6-28 weeks.	Moderate

HDL = high-density lipoprotein; LDL = low-density lipoprotein; NA = not applicable

Combined Lipid-Modifying Therapy With Statin and Omega-3 Fatty Acid Versus Intensification of Statin Monotherapy

We identified no relevant studies that included omega-3 fatty acids.

Discussion

Key Findings and Implications

The evidence suggests that some combination therapy regimens may confer benefits with respect to lowering LDL-c including bile acid sequestrants (up to 14 percent greater LDL-c reduction) and ezetimibe (up to 21 percent greater LDL-c reduction). LDL-c is an important factor in the development of atherosclerotic cardiovascular disease and higher levels of LDL-c have been associated with greater risk of this disease.[7,8] However, there is insufficient evidence to address whether these LDL-c lowering benefits achieved with these medications translate into decreased rates of atherosclerotic cardiovascular disease. Prior trials comparing combination regimens to statin monotherapy such as ENHANCE, AIM-HIGH, and ACCORD-lipid have demonstrated that combination therapy can lead to superior lipid outcomes, but fail to reduce clinical outcomes such as cardiovascular death, MI, revascularization, or stroke.[47,51,53]

We also found that some combination therapy regimens may confer benefts with respect to raising HDL-c including ezetimibe and niacin (up to 6 percent and up to 27 percent, respectively). In particular, given that only one prior study has demonstrated benefit of pharmacologically raising HDL-c with respect to prevention of CVD events**,** the potential long-term clinical benefits of these combination regimens with respect to their HDL-c effects is unclear.[12]

The strength of evidence for all observed comparisons in general populations is provided in Table 26 and in subgroups in Table 27. Most trials included in this report were of relatively short duration (<3 months). In this limited timeframe, investigators are unlikely to capture any changes in a chronic condition like atherosclerotic cardiovascular disease, which typically develops and progresses over a number of years. Powering such studies is especially difficult, given that both arms are taking statins which would reduce the baseline incidence of cardiovascular events. Therefore currently it is not possible to draw conclusions about the clinical implications of the surrogate marker changes identified. However, until additional data are available, these results may help healthcare providers tailor lipid-modifying regimens based on individual patient needs and concerns for adverse events.[129]

Table 26. Summary of the strength of evidence for general populations

Therapy	Potency Comparison (combination therapy vs. monotherapy)	Clinical Events			Serious Adverse Events	Surrogate Markers	
		Mortality	Acute Coronary Events	Revascularization Procedures		LDL-c	HDL-c
Bile Acid Sequestrant	Low potency combination therapy vs high potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
	Mid potency combination therapy vs high potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
	Low potency combination therapy vs mid potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	**MODERATE Combination therapy favored with 0-14% greater LDL reduction**	Insufficient
Ezetimibe	Low potency combination therapy vs high potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	**LOW Combination therapy favored with 2 to 12% greater LDL reduction**	**LOW Combination therapy favored with up to 5 to 6% greater increase in HDL**
	Mid potency combination therapy vs high potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	**MODERATE Combination therapy favored with 3 to 14% greater LDL reduction**	**LOW Combination therapy favored with 2 to 6% greater increase in HDL**
	Low potency combination therapy vs mid potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	**MODERATE Combination therapy favored with 3 to 11% greater LDL reduction**	**LOW Combination therapy favored with 3 to 4% greater increase in HDL**

Table 26. Summary of the strength of evidence for general populations (continued)

Therapy	Potency Comparison (combination therapy vs. monotherapy)	Clinical Events			Serious Adverse Events	Surrogate Markers	
		Mortality	Acute Coronary Events	Revascularization Procedures		LDL-c	HDL-c
Fibrates	Low potency combination therapy vs high potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
	Mid potency combination therapy vs high potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
	Low potency combination therapy vs high potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Niacin	Low potency combination therapy vs high potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
	Mid potency combination therapy vs high potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
	Low potency combination therapy vs mid potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	**MODERATE Combination therapy favored with 15-27% greater increase in HDL**
Omega-3 Fatty Acid	Low potency combination therapy vs high potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
	Mid potency combination therapy vs high potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
	Low potency combination therapy vs mid potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient

HDL = high-density lipoprotein; LDL = low-density lipoprotein
Note: Comparisons for which there was evidence are shown in bold.

Table 27. Summary of the strength of evidence for subgroups

Subgroup	Combination Agent	Potency Comparison (combination therapy vs. monotherapy)	Clinical Events			Serious Adverse Events	Surrogate Markers	
			Mortality	Acute Coronary Events	Revascularization Procedures	Serious Adverse Events	LDL-c	HDL-c
Preexisting CHD	Ezetimibe	Low potency combination therapy vs high potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
		Mid potency combination therapy vs high potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	**MODERATE Combination therapy favored with 5 to 15% greater LDL reduction**	**LOW No between group difference in raising HDL**
		Low potency combination therapy vs mid potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
	Fibrates	Mid potency combination therapy vs high potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Diabetes	Ezetimibe	Low potency combination therapy vs high potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
		Mid potency combination therapy vs high potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	MODERATE Combination therapy favored with 3 to 21% greater LDL reduction	MODERATE Combination therapy favored with 2 to 6% greater increase in HDL
		Low potency combination therapy vs mid potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
	Fibrates	Low potency combination therapy vs mid potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient

CHD = coronary heart disease; LDL = low-density lipoprotein

Note: Comparisons for which there was evidence are shown in bold.

Evidence

Combination Therapy With Bile Acid Sequestrant and Statin Compared to Intensification of Statin Monotherapy

Six randomized trials (410 participants) were identified. There is insufficient evidence to compare the benefits of combined lipid-modifying therapy with a bile acid sequestrant and statin to intensification of statin monotherapy on long-term clinical outcomes or harms, regardless of statin potency.

The results from four trials comparing low potency statin in combination with a bile acid sequestrant to mid potency statin monotherapy (288 participants) suggest that this combination lowers LDL-c up to 14 percent more than mid potency statin monotherapy (SOE: moderate). Evidence for other potency comparisons and outcomes was insufficient.

Combination Therapy With Ezetimibe and Statin Compared to Intensification of Statin Monotherapy

Forty randomized trials (10,955 participants) were identified. Evidence for all clinical outcomes was insufficient, but there was some evidence that combination therapy may have impact on LDL-c and HDL-c. Results from 13 trials suggest that low potency statin in combination with ezetimibe more effectively lowers LDL-c and raises HDL-c as compared to high potency statin monotherapy among general populations (SOE: low for both). Results from 11 trials suggest that mid potency statin combined with ezetimibe more effectively lowers LDL-c and raises HDL-c as compared to high potency statin monotherapyamong general populations (SOE: moderate and low, respectively). Finally, results from six trials suggest that low potency statin in combination with ezetimibe more effectively lowers LDL-c and raises HDL-c as compared to mid potency statin monotherapy (SOE: moderate and low, respectively).

We also identified data on surrogate markers in special populations. Twleve trials among patients with preexisting coronary heart disease favored mid potency statin in combination with ezetimibe for lowering LDL-c as compared to high potency statin monotherapy (SOE: moderate). Four trials among patients with diabetes mellitus also favored mid potency statin plus ezetimbe to a high potency statin monotherapy for lowering LDL-c and raising HDL-c (SOE: moderate for both). Unfortunately, there was insufficient evidence to evaluate harms among the coronary heart disease and diabetes subgroups.

Combination Therapy With Fibrate and Statin Compared to Intensification of Statin Monotherapy

No trials evaluated the benefits of combined lipid-modifying therapy with fibrate and statin to intensification of statin monotherapy on long-term clinical outcomes or serious adverse events, regardless of statin potency. Four randomized trials (1341 participants) assessed surrogate lipid outcomes among different potency comparisons, but provided insufficient evidence to draw conclusions.

Combination Therapy With Niacin and Statin Compared to Intensification of Statin Monotherapy

Five randomized trials (612 participants) were identified. There is insufficient evidence to compare the benefits of combined lipid-modifying therapy with niacin and statin to intensification of statin monotherapy, regardless of statin potency, on long-term clinical outcomes or adverse events, because these endpoints were not reported or the event rates were too low.

Three trials (247 participants) provide insufficient evidence regarding LDL-c,but moderate evidence that combination therapy with niacin and low potency statin raises HDL-c up to 27 percent more than mid potency statin monotherapy (SOE: moderate).

Combination Therapy With Omega-3 Fatty Acid and Statin Compared to Intensification of Statin Monotherapy

No trials were identified that compared a combination of Omega-3 fatty acid with statin to intensification of statin monotherapy; therefore, the strength of evidence is insufficient for all outcomes.

Important Unanswered Questions

Which of the Key Questions Remain Unanswered?

We sought to identify evidence assessing the long-term benefits and serious harms between combination therapy and intensification of statin monotherapy. Unfortunately, we identified only a few studies that reported mortality and serious adverse events with ezetimibe combined with statin as compared to higher potency statin monotherapy. These trials all lasted less than 12 weeks and very few events were reported. We found very limited evidence regarding these long-term benefits and serious harms among other combination therapy comparisons (bile acid sequestrants, fibrates, niacin, and omega-3 fatty acids). Overall, we are unable to conclude whether there are any long-term advantages or serious disadvantages to combination therapy with any agent as compared to intensification of statin monotherapy.

Few studies specifically evaluated high-risk subgroups of interest, which included patients with prior cardiovascular disease or patients with diabetes mellitus. Only comparisons of mid potency statin in combination with ezetimibe to high potency statin monotherapy had sufficient number of trials for evaluation. Among these trials, the strength of evidence is moderate in favor of combination therapy with ezetimibe for lowering LDL-c as compared to statin monotherapy, although we found insufficient evidence with respect to long-term clinical outcomes. Providers could consider combination therapy with ezetimibe as an alternative in diabetic patients who cannot tolerate high or moderate dose statin monotherapy, as recommended by the 2013 cholesterol treatment guidelines.[130] Given that these guidelines have prioritized patient subgroups including those with preexisting atherosclerotic CVD or diabetes aged 40-75, future studies should consider comparing combination therapy (bile acid sequestrants, fibrates, niacin, omega-3 fatty acids) to intensification of statin monotherapy in these high-risk populations.

Very few studies included only elderly individuals (age>75), females, blacks, Asians or Hispanics. No studies included only Native Americans. Given the cardiovascular disease disparities identified among Black and Native American populations,[4] future studies should consider targeting these populations comparing combination therapy to intensification of statin monotherapy as these populations may be more likely to require an aggressive lipid-modifying regimen.

Add-On Combination Lipid-Modifying Therapy Versus Statin Monotherapy

A related question, which this review does not address, is whether adding on another lipid-modifying agent to same the potency statin therapy improves clinical outcomes. Since 2008, several large studies (ACCORD, AIM-HIGH, HSP-2 THRIVE, ENHANCE) have examined this question. The ACCORD trial was designed to detect differences in non-fatal MI, non-fatal stroke, and CVD death among patients treated with statin alone vs. statin with fenofibrate, and found no reduction in events with combination therapy.[51] Similarly, AIM-HIGH compared CHD death, non-fatal MI, ischemic stroke, hospitalization for ACS, and symptom-driven revascularization among patients treated with statin (+/- ezetimibe) vs. statin (+/- ezetimibe) with niacin.[47] Again, there was no additional benefit of adding niacin therapy to the background regimen. HSP2-THRIVE, which tested statin alone vs. statin with niacin/laropiprant was stopped early due to increased side effects with niacin/laropiprant. There was no reduction in MI, stroke, or revascularization with combination therapy.[131] A study of the effect of statin vs. statin + ezetimibe on carotid intima media thickness showed no difference between the treatment groups.[53] The IMPROVE-IT trial, which has enrolled over 18,000 patients and is expected to be completed in September 2014, will examine the effect of statin vs. statin + ezetimibe on CVD events.[52,132] The results of IMPROVE-IT may provide the definitive evidence clinicians seek regarding the clinical effects of ezetimibe. As soon as the results from IMPROVE-IT are released, a new systematic review would be warranted that specificially addresses the question of whether add-on combination therapy or statin monotherapy leads to improved clinical outcomes (Table 28).

For the reader’s reference, we have summarized systematic reviews on combination therapy versus same dose/potency statin that reported on long-term clinical outcomes and/or harms such as serious adverse events or other short-term harms (Table 29).

Table 28. Summary of trials

Trial, Year	Population	Intervention	Clinical Outcomes	Surrogate Outcomes	Adverse Events
ACCORD, 2010[51]	Type 2 DM +/- CVD	Fenofibrate + simvastatin 20-40 mg/d vs. simvastatin 20-40 mg/d	Primary outcome: Major CVD events, non fatal MI, non fatal stroke, CVD death Secondary outcome: Death from any cause, fatal or non fatal congestive heart failure	Total cholesterol, LDL, HDL, TG,	CK elevation, muscle symptoms
AIM-HIGH, 2011[47]	CVD (34% diabetics)	Niacin + simvastatin 40-80 mg/d (+/- EZE 10 mg if needed) vs. simvastatin 40-80 mg/d (+/- EZE 10 mg if needed)	Primary outcome: Coronary heart disease death Nonfatal myocardial infarction Ischemic stroke Hospitalization for acute coronary syndrome Symptom-driven coronary or cerebral revascularization	LDL, HDL	Adherence, elevated LFL, Myalgia, rhabdomyolysis
ENHANCE, 2008[53]	familial hypercholesterolemia	EZE 10 mg +Simvastatin 80 mg Vs. Simvastatin 80 mg	Primary outcomes: carotid-artery intima–media thickness Secondary outcomes: Regression in the mean carotid-artery intima–media thickness, new plaque formation, , mean maximum carotid artery intima-media thickness, mean measures of intima-media thickness of common carotid, carotid bulb, internal carotid artery and femoral artery	LDL, TG, HDL, total cholesterol	Withdrawal due to adverse events, , elevated LFT, CK,

Table 28. Summary of trials (continued)

Trial, Year	Population	Intervention	Clinical Outcomes	Surrogate Outcomes	Adverse Events
HPS2-THRIVE, 2013[131]	pre-existing occlusive arterial disease	ER niacin/ laropiprant + simvastatin 40 mg/d (+/- EZE 10 mg if needed) Vs. simvastatin 40 mg/d (+/- EZE 10 mg if needed)	Primary outcomes: major vascular event' (MVE: a composite of non-fatal MI, coronary death, stroke, or arterial revascularization)- Secondary outcome: serious adverse events	LDL, HDL, TGs	elevated LFT, CK, adherence
IMPROVE-IT (results not published yet)	stabilized high-risk acute coronary syndrome (ACS)	Ezetimibe/ Simvastatin combination (10/40) vs. Simvastatin 40 mg	Primary outcomes: CVD death, non fatal coronary events, unstable angina non fatal stroke, PCI or CABG, angina Secondary outcomes: death due to any cause,	Target LDL,	elevated LFT, CK,

CABG = coronary artery bypass graft; CK = creatinine kinase; CVD = cardiovascular disease; DM = diabetes mellitus; EZE = ezetimibe; HDL = high-density lipoprotein; LDL = low-density lipoprotein; LFT = liver function tests; PCI = percutaneous coronary intervention; TG = triglycerides

Table 29. Systematic reviews on combination therapy versus same dose/potency statin

Author, Year	Population	Intervention	Clinical Outcomes	Surrogate Outcomes	Adverse Events
Guo et al, 2012[133]	Combined hyperlipidemia	Statin monotherapy vs. statin (same dose) + fenofibrate	Serious adverse events	NR	Withdrawal due to adverse events, any adverse event, AST/ALT>3xULN, CK>5xULN
Abramson et al, 2011[134]	Hypercholesterolemia Subgroup: males, females	Statin monotherapy vs. statin + EZE (some studies have same dose statin, others have doubling in monotherapy)	Mortality, serious AE	LDL, non-HDL-c, TGs, HDL	any adverse event, AST/ALT>3xULN, CK>5Xuln, rhabdomyolysis
Mikhailidis et al, 2011[135]	Hypercholesterolemia	Statin monotherapy vs. statin + EZE (some studies have same dose statin, others have doubling in monotherapy)	NR	LDL, non-HDL-c, HDL, LDL target, TC to HDL ratio,	Withdrawal due to AE
Sharma et al, 2009[55]	Dyslipidemia	Statin monotherapy (high dose) Vs. combination (low dose statin)	Mortality, vascular death, serious AE, Cancer	LDL target, LDL, HDL, carotid intima media thickness	Treatment adherence and harm.
Kashani et al, 2008[136]	Hyperlipidemia	Statin monotherapy vs. statin + EZE (some studies have same dose statin, others have doubling in monotherapy)	NR	LDL, HDL, TGs	Myalgia, CK, AST/ALT elevations, rhabdomyolysis, Discontinuations due to adverse events
Mikhailidis et al, 2007[137]	Hypercholesterolemia, Subgroup: CHD	Statin monotherapy vs. statin (same dose) + EZE	NR	LDL, non-HDL-c, HDL, TG	CK, AST/ALT elevations

AE = Adverse events; AST = aspartate transaminase; ALT = alanine transaminase; CK = creatinine kinase; CHD = cardiovascular heat disease; DM EZE = ezetimibe; HDL = high-density lipoprotein; LDL = low-density lipoprotein; NR = not reported; TG = triglycerides

Findings in Relationship to What Is Already Known

This report is an update of a 2009 AHRQ Effective Healthcare Program comparative effectiveness review. The prior review found a paucity of evidence to address these same key questions, and the authors concluded that there was insufficient evidence to determine whether any combination therapy held benefit over monotherapy.[55,56] We based this update on the prior review; however, a few key differences should be noted. We included only studies with patients of moderate or greater CHD risk who may benefit most from combination therapy or intensification of statin monotherapy, while the prior review included all studies regardless of patient CHD risk. We also categorized statin combination therapy and monotherapy according to individual agents LDL-c lowering potency (low, mid, and high), while the prior review dichotomized agents into low-dose and high-dose. We also required there to be a difference in potency category between the combination therapy and monotherapy arms to reflect a real intensification of statin dose in the monotherapy as compared to the combination arm. These three differences influenced the populations that we included, as well as enabled us to standardize the comparisons of therapeutic regimens across different statin agents. As a result, we excluded many trials from this update that were included in the prior review.

We were able to make conclusions regarding several surrogate clinical markers. Many high profile clinical trials comparing combination therapy agents to statin monotherapy have shown that combination therapy can achieve better lipid outcomes. For example, ezetimibe + high potency simvastatin is more effective at lowering LDL-c than high potency simvastatin monotherapy (ENHANCE) and niacin + high potency simvastatin is more effective at raising HDL-c than high potency simvastatin monotherapy (AIM-HIGH).[47,53] These trials were not included in this review, as they did not meet our potency comparison requirements. In this review, we found moderate strength evidence supporting low potency statin in combination with either bile acid sequestrant or ezetimibe for lowering LDL-c as compared to mid potency statin monotherapy. There is also low strength evidence supporting mid potency statin in combination with ezetimibe for lowering LDL-c as compared to high potency statin monotherapy. Combination therapy with ezetimibe or niacin raised HDL-c, while combination therapy with bile acid sequestrant had no differential effect on HDL-c as compared to statin monotherapy. We could make no conclusions on combination therapy with fibrates or omega-3 fatty acids on these surrogate makers given the few included trials that used these agents.

Applicability

Many trials that met our inclusion criteria were implemented in populations of hyperlipidemic patients, and most were designed to evaluate effects on lipid measures and short-term harms. The results of most trials generalize to patients with hyperlipidemia uncomplicated by other major co-morbid conditions. Interestingly, we identified fewer trials that were conducted among high CHD risk patients such as those with diabetes or preexisting cardiovascular disease. These patients could benefit from improvement in their lipid profiles and are the most likely to be receiving more aggressive lipid-modifying regimens in clinical practice. We only identified adequate numbers of trials comparing mid potency statin in combination with ezetimibe to high potency statin monotherapy in these high-risk populations.

Interventions were similar across studies. It is important to note that many trials employed a medication titration regimen to specify how the doses of each medication should be increased to reach their target. This was especially common among trials with niacin, in order to minimize the medication side effects (flushing). These schedules may have improved the tolerability of the medications in the trial, and clinicians should be aware that a similar approach might need to be taken in clinical practice.

Implications for Clinical and Policy Decisionmaking

These results may help aid individual decision-making and patient management. Our findings may be most applicable to patients who cannot tolerate high-dose statin therapy. The ACC has already released lipid treatment guidelines for patients with stable ischemic heart disease that recommend fibrate or niacin for patients who cannot tolerate statin therapy. Although the studies in our report did not include statin-intolerant patients, perhaps some patients that can tolerate a lower-dose statin with the addition of either bile acid sequestrant or ezetimibe could better achieve additional LDL-lowering. It is unclear whether fibrates, niacin, or omega-3 fatty acids can also have a beneficial LDL-lowering effect in such patients. As noted, we did not include the results from several large trials of an add-on lipid-modifying agent to same potency statin with clinical outcomes, as these studies did not address our key questions. However, these trials showed no clinical benefit of adding an additional agent and our results should be considered within that context when patients and clinicians are considering different lipid-modifying regimens. Clinicians struggle against non-adherence to lipid-modifying therapy, which is common among patients taking these agents.[138] We had insufficient data to assess whether adherence differed between lower-potency combination therapy and higher-dose statin monotherapy, which will be an important aspect to address in future trials. Clinicians would also have to consider tolerability and cost issues with their patients. We did not compare tolerability of the individual add-on agents against each other. Adherence data would potentially serve as a proxy measure of tolerability, however, was not consistently reported. Clinicians would also have to consider the cost of the add-on agents with their patients based on drug formularies, as the cost of these agents vary widely.

These results may also help provide an evidence base for future clinical practice guidelines and policy decisions. However, we suspect that the strength of evidence for most comparisons is too low to support guidelines or policy changes at this time.

Limitations of the Comparative Effectiveness Review Process

This review focused narrowly on combination therapy compared with statin intensification. As a result, many studies of add on combination therapy versus the same statin dose or non-statin monotherapy were excluded, because they did not address the key questions. Given several previous reviews on dietary modification and reduction of lipids and CVD risk, we did not include these therapies in this review.[139,140] Further, we did not examine differences in statin response based on genetic variations.[141,142] We also excluded non-English language publications, although we do not believe this introduced significant bias. While we were able to standardize the potency of different doses of various statins, we were unable to classify the potency of the other lipid-modifying agents used in the combination therapy arms. We noted differential effects on lipid outcomes in some trials where the same potency statin was used in the combination arm, but different doses of the other agent were used.

This report focuses primarily on LDL-c and HDL-c outcomes due to the available evidence and strategy recommended by the clinical practice guideline at the time this review was conducted. The 2013 cholesterol treatment guidelines had yet to be released and clinical practice relied on recommendations of ATP III, which also emphasized these lipid surrogates. Due to this timing issue, we were also unable to specify the four “statin benefit groups” as our primary populations of interest in this review, although we do believe that we have captured the majority of populations in this report. Additionally, our potency categorizations differ slightly from those in the guidelines.

Strengths and Limitations of the Evidence Base

The strength of evidence was insufficient for many comparisons and outcomes due to a paucity of studies and poor quality of exisiting studies. Trials were frequently downgraded in risk of bias assessment for lack of blinding by participant and study personnel (performance bias), for not reporting the blinding of outcome assessors (detection bias), or for not accounting for losses to followup or handling of incomplete data (attrition bias). Few studies reported variance estimates for the between group differences in any outcomes over time. In some instances, the studies did not report a mean difference or point estimate stating only that there was no significant difference between the groups. In addition, some studies did not report an intention-to-treat analysis and others did not specify the number analyzed in each arm. All of these factors limited our ability to conduct meta-analyses. Where we conducted meta-analysis, substantial heterogeneity was present in most cases.

The evidence base was also limited due to the short duration of most studies. Most trials we identified were of relatively short duration, despite the fact that these medications are currently used in clinical practice as chronic, long-term medications. Many studies either did not evaluate or were of insufficient duration to adequately assess long-term clinical outcomes including mortality, acute coronary events, and revascularization procedures or tolerability of or persistence to the medication regimen. Studies often pooled results on adverse effects across arms, which limited our ability to determine whether different doses and potencies of combination and monotherapy led to different rates of these events. Ultimately, clinicians hope to reduce the likelihood of negative clinical events for their patients by achieving their lipid goals with medications while minimizing the risk for side effects and harms. Providing evidence that compares combination therapy and intensification of statin monotherapy with respect to these important clinical outcomes, tolerability, and harms would aid decision-making for clinicians and highlight for patients the health benefits of adhering to these regimens.

Future Research Needs

We suggest that most comparisons and outcomes that have low or insufficient evidence are future research needs. In order to answer whether there are long-term benefits with respect to mortality, acute coronary events, and revascularization procedures, future investigators need to make these endpoints the primary outcomes of their trials and ensure that trials are of sufficient duration to actually capture these events (at least 12 months or preferably longer). Recent trials such as ENHANCE, ACCORD, and AIM-HIGH have failed to show any additional clinical benefit of combination therapy as compared to statin monotherapy.[47,51,53] While the forthcoming IMPROVE-IT trial may be able to clarify whether ezetimibe + simvastatin is superior to simvastatin alone with respect to cardiovascular deaths, MI or strokes, this trial uses equivalent doses of simvastatin in the combination and monotherapy arms.[52] This trial will not provide information to make decisions about the effectiveness of intensification of statin monotherapy compared to combination therapy. Therefore, additional trials to answer this specific question that are of sufficient duration to capture these outcomes are needed. Trials of longer duration would also better reflect how these medications are currently used in clinical practice, where they are considered chronic use medications. These trials could evaluate outcomes relevant to medication persistence such as tolerability, side effects, and serious adverse events.

We further suggest that future studies focus on high-risk CHD populations and populations with greater burden of cardiovascular disease to determine which strategy provides better short-term improvements in lipid profile and long-term clinical benefits. These populations would include patients with diabetes and preexisting cardiovascular disease, as well as Black and Native American populations.[4] It may be worthwhile to explore differences between men and women, as the ACCORD trial showed benefit of combination therapy with fibrate in men and potential harms with this combination therapy in women.[51] These studies would have tremendous impact on clinical practice, as these patients are the most likely to need a more aggressive lipid-modifying regimen.

The current head-to-head comparisons of a combination regimen to intensification of statin therapy cannot help clinicians decide between different combination therapy options. The next step to inform clinical decisionmaking would be to help clinicians in selecting the most appropriate lipid-modifying regimen from all available options. We suggest that future studies conduct head-to-head comparisons of multiple combination regimens against each other as well as intensification of statin monotherapy to address this need. Studies are needed that examine whether patients who are unable to tolerate high-potency statin monotherapy could achieve LDL-c and CVD reductions with combination therapy that are consistent with potent statins (50-60%). Furthermore, it would be useful to deteremine if LDL-c lowering of 50% achieved with a statin and a bile acid sequestrant is as efficacious as a statin and ezetimibe, and whether both are as efficacious as a potent statin alone. Finally, alternative study designs such as observational studies using registry data from electronic medical records could provide useful data on long-term or rare clinical outcomes. A number of trials have shown that non-statin lipid modifying medications may not improve or even potentially worsen some clinical outcomes. Future studies may need to consider including non-statin monotherapy as another comparison group with respect to clinical outcomes and harms. Such information would be informative to clinicians who may be considering non-statin monotherapy as a treatment option.

There are design and reporting considerations that should be considered for future studies. Intervention trials should be of sufficient duration to assess the efficacy of interventions on long-term clinical outcomes like mortality, acute coronary events, and revascularization procedures. We suggest that one-year should be a minimum duration of followup for these interventions. We would also encourage future studies to report variance estimates for all outcomes, as well as account for losses to followup by arm and report the number analyzed in each arm. Finally, we would also encourage studies to report adverse event outcomes by individual arm, rather than reporting only pooled results. Different doses and potencies of therapeutic regimens result in differential side effects and harms and this would be important to capture.

Conclusions

Although many studies looked at intermediate outcomes, few studies addressed the question of which approach produces better clinical outcomes. Combination of statin with ezetimibe or bile acid sequestrant lowered LDL-c better than intensification of statin monotherapy, but evidence for clinical outcomes (mortality, acute coronary events, and revasculartization procedures) was insufficient across all potency comparisons for all combination therapy regimens. Additional studies evaluating long-term clinical benefits and harms are needed to better inform clinical decisionmaking, patient choice, and clinical practice guidelines.

References

1. Go AS, Mozaffarian D, Roger VL et al. Heart disease and stroke statistics--2013 update: a report from the American Heart Association. Circulation 2013; 127(1):e6-e245. PMID: 23239837

2. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002; 106(25):3143-421. PMID: 12485966

3. Heidenreich PA, Trogdon JG, Khavjou OA et al. Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. Circulation 2011; 123(8):933-44. PMID: 21262990

4. Liao Y, Bang D, Cosgrove S et al. Surveillance of health status in minority communities - Racial and Ethnic Approaches to Community Health Across the U.S. (REACH U.S.) Risk Factor Survey, United States, 2009. MMWR Surveill Summ 2011; 60(6):1-44. PMID: 21597458

5. Mosca L, Barrett-Connor E, Wenger NK. Sex/gender differences in cardiovascular disease prevention: what a difference a decade makes. Circulation 2011; 124(19):2145-54. PMID: 22064958

6. Berliner JA, Navab M, Fogelman AM et al. Atherosclerosis: basic mechanisms. Oxidation, inflammation, and genetics. Circulation 1995; 91 (9):2488-96. PMID: 7729036

7. Cui Y, Blumenthal RS, Flaws JA et al. Non-high-density lipoprotein cholesterol level as a predictor of cardiovascular disease mortality. Arch Intern Med 2001; 161(11):1413-9. PMID: 11386890

8. Pekkanen J, Linn S, Heiss G et al. Ten-year mortality from cardiovascular disease in relation to cholesterol level among men with and without preexisting cardiovascular disease. N Engl J Med 1990; 322(24):1700-7. PMID: 2342536

9. Barter P, Gotto AM, LaRosa JC et al. HDL cholesterol, very low levels of LDL cholesterol, and cardiovascular events. N Engl J Med 2007; 357(13):1301-10. PMID: 17898099

10. Maron DJ. The epidemiology of low levels of high-density lipoprotein cholesterol in patients with and without coronary artery disease. Am J Cardiol 2000; 86(12A):11L-4L. PMID: 11374848

11. Di Angelantonio E, Sarwar N, Perry P et al. Major lipids, apolipoproteins, and risk of vascular disease. JAMA 2009; 302(18):1993-2000. PMID: 19903920

12. Robins SJ, Collins D, Wittes JT, Papademetriou V,et. al. VA-HIT Study Group. Veterans Affairs High-Density Lipoprotein Intervention Trial. Relation ofgemfibrozil treatment and lipid levels with major coronary events: VA-HIT: arandomized controlled trial. JAMA 2001; 285(12):1585-91. PMID: 11268266

13. Endo A, Tsujita Y, Kuroda M, Tanzawa K. Inhibition of cholesterol synthesis in vitro and in vivo by ML-236A and ML-236B, competitive inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase. Eur J Biochem 1977; 77(1):31-6. PMID: 908337

14. Brown MS, Goldstein JL. A receptor-mediated pathway for cholesterol homeostasis. Science 1986; 232(4746):34-47. PMID: 3513311

15. Ginsberg HN, Le NA, Short MP, Ramakrishnan R, Desnick RJ. Suppression of apolipoprotein B production during treatment of cholesteryl ester storage disease with lovastatin. Implications for regulation of apolipoprotein B synthesis. J Clin Invest 1987; 80(6):1692-7. PMID: 3680522

16. Grundy SM. Consensus statement: Role of therapy with "statins" in patients with hypertriglyceridemia. Am J Cardiol 1998; 81(4A):1B-6B. PMID: 9526806

17. Bakker-Arkema RG, Davidson MH, Goldstein RJ et al. Efficacy and safety of a new HMG-CoA reductase inhibitor, atorvastatin, in patients with hypertriglyceridemia. JAMA 1996; 275(2):128-33. PMID: 8531308

18. Stein EA, Lane M, Laskarzewski P. Comparison of statins in hypertriglyceridemia. Am J Cardiol 1998; 81(4A):66B-9B. PMID: 9526817

19. Baigent C, Blackwell L, Emberson J et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet 2010; 376(9753):1670-81. PMID: 21067804

20. Corti R, Fayad ZA, Fuster V et al. Effects of lipid-lowering by simvastatin on human atherosclerotic lesions: a longitudinal study by high-resolution, noninvasive magnetic resonance imaging. Circulation 2001; 104(3):249-52. PMID: 11457739

21. Schartl M, Bocksch W, Koschyk DH et al. Use of intravascular ultrasound to compare effects of different strategies of lipid-lowering therapy on plaque volume and composition in patients with coronary artery disease. Circulation 2001; 104(4):387-92. PMID: 11468198

22. Ridker PM, Rifai N, Pfeffer MA, Sacks F, Braunwald E. Long-term effects of pravastatin on plasma concentration of C-reactive protein. The Cholesterol and Recurrent Events (CARE) Investigators. Circulation 1999; 100(3):230-5. PMID: 10411845

23. Egashira K, Hirooka Y, Kai H et al. Reduction in serum cholesterol with pravastatin improves endothelium-dependent coronary vasomotion in patients with hypercholesterolemia. Circulation 1994; 89(6):2519-24. PMID: 8205659

24. Shepherd J, Cobbe SM, Ford I et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. N Engl J Med 1995; 333(20):1301-7. PMID: 7566020

25. Downs JR, Clearfield M, Weis S et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. JAMA 1998; 279(20):1615-22. PMID: 9613910

26. Sever PS, Dahlof B, Poulter NR et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial--Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. Lancet 2003; 361(9364):1149-58. PMID: 12686036

27. Ridker PM, Danielson E, Fonseca FA et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008; 359(21):2195-207. PMID: 18997196

28. LaRosa JC, Grundy SM, Waters DD et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med 2005; 352(14):1425-35. PMID: 15755765

29. Sacks FM, Pasternak RC, Gibson CM, Rosner B, Stone PH. Effect on coronary atherosclerosis of decrease in plasma cholesterol concentrations in normocholesterolaemic patients. Harvard Atherosclerosis Reversibility Project (HARP) Group. Lancet 1994; 344(8931):1182-6. PMID: 7934538

30. Taylor F, Ward K, Moore TH et al. Statins for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev 2011; (1):CD004816. PMID: 21249663

31. Preiss D, Seshasai SR, Welsh P, Murphy SA et. al. Risk of incident diabetes withintensive-dose compared with moderate-dose statin therapy: a meta-analysis. JAMA 2011; 305(24):2556-64. PMID: 21693744

32. Graham DJ, Staffa JA, Shatin D, Andrade SE et. al. Incidence of hospitalized rhabdomyolysis inpatients treated with lipid-lowering drugs. JAMA 2004; 292(21):2585-90. PMID: 15572716

33. FDA Drug Safety Communication: New restrictions, contraindications, and dose limitations for Zocor (simvastatin) to reduce the risk of muscle injury [Web Page]. Available at http://www.fda.gov/Drugs/DrugSafety/ucm256581.htm. (Accessed 27 September 2013).

34. Einarsson K, Ericsson S, Ewerth S et al. Bile acid sequestrants: mechanisms of action on bile acid and cholesterol metabolism. Eur J Clin Pharmacol 1991; 40 Suppl 1:S53-8. PMID: 2044645

35. Sudhop T, Lutjohann D, Kodal A et al. Inhibition of intestinal cholesterol absorption by ezetimibe in humans. Circulation 2002; 106(15):1943-8. PMID: 12370217

36. Sweeney ME, Johnson RR. Ezetimibe: an update on the mechanism of action, pharmacokinetics and recent clinical trials. Expert Opin Drug Metab Toxicol 2007; 3(3):441-50. PMID: 17539750

37. Dujovne CA, Ettinger MP, McNeer JF et al. Efficacy and safety of a potent new selective cholesterol absorption inhibitor, ezetimibe, in patients with primary hypercholesterolemia. Am J Cardiol 2002; 90(10):1092-7. PMID: 12423709

38. Knopp RH, Gitter H, Truitt T et al. Effects of ezetimibe, a new cholesterol absorption inhibitor, on plasma lipids in patients with primary hypercholesterolemia. Eur Heart J 2003; 24(8):729-41. PMID: 12713767

39. Staels B, Dallongeville J, Auwerx J, Schoonjans K, Leitersdorf E, Fruchart JC. Mechanism of action of fibrates on lipid and lipoprotein metabolism. Circulation 1998; 98(19):2088-93. PMID: 9808609

40. Knopp RH, Ginsberg J, Albers JJ et al. Contrasting effects of unmodified and time-release forms of niacin on lipoproteins in hyperlipidemic subjects: clues to mechanism of action of niacin. Metabolism 1985; 34(7):642-50. PMID: 3925290

41. Probstfield JL, Hunninghake DB. Nicotinic acid as a lipoprotein-altering agent. Therapy directed by the primary physician. Arch Intern Med 1994; 154(14):1557-9. PMID: 8031204

42. Illingworth DR, Stein EA, Mitchel YB et al. Comparative effects of lovastatin and niacin in primary hypercholesterolemia. A prospective trial. Arch Intern Med 1994; 154(14):1586-95. PMID: 8031206

43. Canner PL, Berge KG, Wenger NK et al. Fifteen year mortality in Coronary Drug Project patients: long-term benefit with niacin. J Am Coll Cardiol 1986; 8(6):1245-55. PMID: 3782631

44. Bays H. Clinical overview of Omacor: a concentrated formulation of omega-3 polyunsaturated fatty acids. Am J Cardiol 2006; 98(4A):71i-6i. PMID: 16919519

45. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico. Lancet 1999; 354(9177):447-55. PMID: 10465168

46. Deedwania P, Stone PH, Bairey Merz CN et al. Effects of intensive versus moderate lipid-lowering therapy on myocardial ischemia in older patients with coronary heart disease: results of the Study Assessing Goals in the Elderly (SAGE). Circulation 2007; 115(6):700-7. PMID: 17283260

47. Boden WE, Probstfield JL, Anderson T et al. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. N Engl J Med 2011; 365(24):2255-67. PMID: 22085343

48. Mazze RS, Strock ES, Monk AM, et. a. Diurnal glucose profiles using continuous glucose monitoring to identify the glucose-loweringcharacteristics of colesevelam HCl (Welchol). Endocr Pract 2013; 19 (2):275-83. PMID: 23598534

49. Brown BG, Zhao XQ, Chait A et al. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. N Engl J Med 2001; 345(22):1583-92. PMID: 11757504

50. Taylor AJ , Villines TC, Stanek EJ et al. Extended-release niacin or ezetimibe and carotid intima-media thickness. N Engl J Med 2009; 361(22):2113-22. PMID: 19915217

51. Ginsberg HN, Elam MB, Lovato LC et al. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med 2010; 362(17):1563-74. PMID: 20228404

52. Cannon CP, Giugliano RP, Blazing MA, Harrington RA, et. al. IMPROVE-IT Investigators. Rationale and design of IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial): comparison of ezetimbe/simvastatin versus simvastatin monotherapy on cardiovascular outcomes in patients with acute coronary syndromes. Am Heart J. 2008; 156(5):826-32. PMID: 19061694

53. Kastelein JJ, Akdim F, Stroes ES, Zwinderman AH, et.al. ENHANCE Investigators. Simvastatin with or without ezetimibe in familial hypercholesterolemia. N Engl J Med. 2008; 358(14):1431-43. PMID: PMID: 18376000

54. Fihn SD, Gardin JM, Abrams J, Berra K, et. al. American College of Cardiology Foundation/American Heart Association Task Force. ACCF/AHA/ACP/AATS/PCNA/ SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. Circulation 2012; 126(25). PMID: 23166211

55. Sharma M, Ansari MT, Abou-Setta AM et al. Systematic review: comparative effectiveness and harms of combination therapy and monotherapy for dyslipidemia. Ann Intern Med 2009; 151(9):622-30. PMID: 19884623

56. Sharma M, Ansari MT, Soares-Weiser K et al. Comparative Effectiveness of Lipid-Modifying Agents [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2009. 2009 . PMID: 20704039

57. Tsertsvadze A MM, Chou, R, Garritty C, et. al. Comparative Effectiveness Reviews: Current Efforts in AHRQ's Effective Health Care Program. Methods Guide for Comparative Effectiveness Reviews. (Prepared by the University of Ottawa EPC, RAND CorporationSouthern California EPC, Oregon EPC, University of Connecticut EPC, RTIUniversity of North Carolina EPC, Johns Hopkins Bloomberg School of Public Health EPC under Contract No. 290-02-0021 EPC2). AHRQ Publication No. 11-EHC057-EF. Rockville, MD: Agency for Healthcare Research and Quality. July 2011. Available at: www.effectivehealthcare.ahrq.gov/reports/ final.cfm. 2011

58. Higgins JPT GS. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

59. Weng TC YY, Lin SJ, Tai SH.. A systematic review and meta-analysis on the therapeutic equivalence of statins. J Clin Pharm Ther 2010; 35(2):139-51

60. Maron DJ, Fazio S, Linton MF.. Current perspectives on statins. Circulation 2000; 101(2):207-13.

61. Furukawa TA, Barbui C, Cipriani A, Brambilla P, Watanabe N.. Imputing missing standard deviations in meta-analyses can provide accurate results. J Clin Epidemiol 2006; 59(1):7-10.

62. DerSimonian R LN. Meta-analysis in clinical trials. Control Clin Trials 1986; 7(3):177-88.

63. Owens DK LK ADeal. AHRQ series paper 5: grading the strength of a body of evidence when comparing medical interventions--agency for healthcare research and quality and the effective health-care program. J Clin Epidemiol. 2010; 63(5):513-23.

64. Martin SS, Blaha MJ, Elshazly MB, Brinton EA. Friedewald Estimated versus Directly Measured Low-Density Lipoprotein Cholesterol and Treatment Implications. J Am Coll Cardiol 2013; S0735-1097.

65. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Rockville, MD: Agency for Healthcare Research and Quality; April 2012. AHRQ Publication No. 10(11)-EHC063-EF. Chapters available at: www.effectivehealthcare.ahrq.gov.

66. Ballantyne CM, Abate N, Yuan Z, King TR, Palmisano J. Dose-comparison study of the combination of ezetimibe and simvastatin (Vytorin) versus atorvastatin in patients with hypercholesterolemia: the Vytorin Versus Atorvastatin (VYVA) study. Am Heart J 2005; 149(3):464-73. PMID: 15864235

67. Bays HE, Ose L, Fraser N et al. A multicenter, randomized, double-blind, placebo-controlled, factorial design study to evaluate the lipid-altering efficacy and safety profile of the ezetimibe/simvastatin tablet compared with ezetimibe and simvastatin monotherapy in patients with primary hypercholesterolemia. Clin Ther 2004; 26(11):1758-73. PMID: 15639688

68. Davidson MH, McGarry T, Bettis R et al. Ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia. J Am Coll Cardiol 2002; 40(12):2125-34. PMID: 12505224

69. Goldberg AC, Sapre A, Liu J, Capece R, Mitchel YB. Efficacy and safety of ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia: a randomized, double-blind, placebo-controlled trial. Mayo Clin Proc 2004; 79(5):620-9. PMID: 15132403

70. Athyros VG, Papageorgiou AA, Athyrou VV, Demitriadis DS, Pehlivanidis AN, Kontopoulos AG. Atorvastatin versus four statin-fibrate combinations in patients with familial combined hyperlipidaemia. J Cardiovasc Risk 2002; 9(1):33-9. PMID: 11984215

71. Ahmed S, Ullah E, Ahmed M, Abbas R, Khan MA, Iqbal J. Efficacy of combination of ezetimibe and simvastatin versus atorvastatin in reducing low density lipoprotein-cholesterol in male patients of hypercholesterolemia, at Bahawalpur. Medical Forum Monthly 2008; 19(5):3-9.

72. Araujo DB, Bertolami MC, Ferreira WP et al. Pleiotropic effects with equivalent low-density lipoprotein cholesterol reduction: comparative study between simvastatin and simvastatin/ezetimibe coadministration. J Cardiovasc Pharmacol 2010; 55(1):1-5. PMID: 19770669

73. Florentin M, Liberopoulos EN, Moutzouri E, Rizos CV, Tselepis AD, Elisaf MS. The effect of simvastatin alone versus simvastatin plus ezetimibe on the concentration of small dense low-density lipoprotein cholesterol in subjects with primary hypercholesterolemia. Curr Med Res Opin 2011; 27(3):685-92. PMID: 21271793

74. Lee SH, Kang SM, Park S, Jang Y, Chung N, Choi D. The effects of statin monotherapy and low-dose statin/ezetimibe on lipoprotein-associated phospholipase A(2). Clin Cardiol 2011; 34 (2):108-12. PMID: 21298654

75. Lee SH, Park S, Kang SM, Jang Y, Chung N, Choi D. Effect of atorvastatin monotherapy and low-dose atorvastatin/ezetimibe combination on fasting and postprandial triglycerides in combined hyperlipedemia. J Cardiovasc Pharmacol Ther 2012; 17(1):65-71. PMID: 21386036

76. Liberopoulos EN, Makariou SE, Moutzouri E, Kostapanos MS, Challa A, Elisaf M. Effect of Simvastatin/Ezetimibe 10/10 mg Versus Simvastatin 40 mg on Serum Vitamin D Levels. J Cardiovasc Pharmacol Ther 2013. PMID: 23288870

77. Moutzouri E, Liberopoulos E, Mikhailidis DP et al. Comparison of the effects of simvastatin vs. rosuvastatin vs. simvastatin/ezetimibe on parameters of insulin resistance. Int J Clin Pract 2011; 65(11):1141-8. PMID: 21995692

78. Moutzouri E, Tellis CC, Rousouli K et al. Effect of simvastatin or its combination with ezetimibe on Toll-like receptor expression and lipopolysaccharide - induced cytokine production in monocytes of hypercholesterolemic patients. Atherosclerosis 2012; 225(2):381-7. PMID: 23062767

79. Rudofsky G, Reismann P, Groener JB et al. Identical LDL-cholesterol lowering but non-identical effects on NF-kappaB activity: High dose simvastatin vs combination therapy with ezetimibe. Atherosclerosis 2012; 223(1):190-6. PMID: 22633472

80. Her AY, Kim JY, Kang SM et al. Effects of atorvastatin 20 mg, rosuvastatin 10 mg, and atorvastatin/ezetimibe 5 mg/5 mg on lipoproteins and glucose metabolism. J Cardiovasc Pharmacol Ther 2010; 15(2):167-74. PMID: 20147603

81. Airan-Javia SL, Wolf RL, Wolfe ML, Tadesse M, Mohler E, Reilly MP. Atheroprotective lipoprotein effects of a niacin-simvastatin combination compared to low- and high-dose simvastatin monotherapy. Am Heart J 2009; 157(4):687.e1-8. PMID: 19332196

82. Hunninghake D, Insull W Jr, Toth P, Davidson D, Donovan JM, Burke SK. Coadministration of colesevelam hydrochloride with atorvastatin lowers LDL cholesterol additively. Atherosclerosis 2001; 158(2):407-16. PMID: 11583720

83. Johansson J. Low-dose combination therapy with colestipol and simvastatin in patients with moderate to severe hypercholesterolaemia. 5. 1995:39-44.

84. Ballantyne CM, Houri J, Notarbartolo A et al. Effect of ezetimibe coadministered with atorvastatin in 628 patients with primary hypercholesterolemia: a prospective, randomized, double-blind trial. Circulation 2003; 107(19):2409-15. PMID: 12719279

85. Barrios V , Amabile N, Paganelli F et al. Lipid-altering efficacy of switching from atorvastatin 10 mg/day to ezetimibe/simvastatin 10/20 mg/day compared to doubling the dose of atorvastatin in hypercholesterolaemic patients with atherosclerosis or coronary heart disease. Int J Clin Pract 2005; 59(12):1377-86. PMID: 16351668

86. Catapano AL, Davidson MH, Ballantyne CM et al. Lipid-altering efficacy of the ezetimibe/simvastatin single tablet versus rosuvastatin in hypercholesterolemic patients. Curr Med Res Opin 2006; 22(10):2041-53. PMID: 17022864

87. Constance C, Westphal S, Chung N et al. Efficacy of ezetimibe/simvastatin 10/20 and 10/40 mg compared with atorvastatin 20 mg in patients with type 2 diabetes mellitus. Diabetes Obes Metab 2007; 9(4):575-84. PMID: 17451425

88. Gaudiani LM, Lewin A, Meneghini L et al. Efficacy and safety of ezetimibe co-administered with simvastatin in thiazolidinedione-treated type 2 diabetic patients. Diabetes Obes Metab 2005; 7(1):88-97. PMID: 15642080

89. Goldberg RB, Guyton JR, Mazzone T et al. Ezetimibe/simvastatin vs atorvastatin in patients with type 2 diabetes mellitus and hypercholesterolemia: the VYTAL study. Mayo Clin Proc 2006; 81(12):1579-88. PMID: 17165637

90. McKenney JM, Jones PH, Bays HE et al. Comparative effects on lipid levels of combination therapy with a statin and extended-release niacin or ezetimibe versus a statin alone (the COMPELL study). Atherosclerosis 2007; 192(2):432-7. PMID: 17239888

91. Piorkowski M, Fischer S, Stellbaum C et al. Treatment with ezetimibe plus low-dose atorvastatin compared with higher-dose atorvastatin alone: is sufficient cholesterol-lowering enough to inhibit platelets? J Am Coll Cardiol 2007; 49(10):1035-42. PMID: 17349882

92. Roeters van Lennep HW, Liem AH, Dunselman PH, Dallinga-Thie GM, Zwinderman AH, Jukema JW. The efficacy of statin monotherapy uptitration versus switching to ezetimibe/simvastatin: results of the EASEGO study. Curr Med Res Opin 2008; 24(3):685-94. PMID: 18226326

93. Stein E, Stender S, Mata P et al. Achieving lipoprotein goals in patients at high risk with severe hypercholesterolemia: efficacy and safety of ezetimibe co-administered with atorvastatin. Am Heart J 2004; 148(3):447-55. PMID: 15389231

94. Shah HD, Parikh KH, Chag MC et al. Beneficial effects of the addition of fenofibrate to statin therapy in patients with acute coronary syndrome after percutaneous coronary interventions. Exp Clin Cardiol 2007; 12(2):91-6. PMID: 18650989

95. Bays HE, McGovern ME. Once-daily niacin extended release/lovastatin combination tablet has more favorable effects on lipoprotein particle size and subclass distribution than atorvastatin and simvastatin. Prev Cardiol 2003; 6(4):179-88. PMID: 14605511

96. Yamazaki D, Ishida M, Watanabe H et al. Comparison of anti-inflammatory effects and high-density lipoprotein cholesterol levels between therapy with quadruple-dose rosuvastatin and rosuvastatin combined with ezetimibe. Lipids Health Dis 2013; 12(1):9. PMID: 23374898

97. Bardini G, Giorda CB, Pontiroli AE, Le Grazie C, Rotella CM. Ezetimibe + simvastatin versus doubling the dose of simvastatin in high cardiovascular risk diabetics: a multicenter, randomized trial (the LEAD study). Cardiovasc Diabetol 2010; 9:20. PMID: 20492655

98. Ben-Yehuda O, Wenger NK, Constance C et al. The comparative efficacy of ezetimibe added to atorvastatin 10 mg versus uptitration to atorvastatin 40 mg in subgroups of patients aged 65 to 74 years or greater than or equal to 75 years. J Geriatr Cardiol 2011; 8(1):1-11. PMID: 22783278

99. Zieve F, Wenger NK, Ben-Yehuda O et al. Safety and efficacy of ezetimibe added to atorvastatin versus up titration of atorvastatin to 40 mg in Patients > or = 65 years of age (from the ZETia in the ELDerly. Am J Cardiol 2010; 105(5):656-63. PMID: 20185012

100. Cho YK, Hur SH, Han CD et al. Comparison of Ezetimibe/Simvastatin 10/20 mg Versus Atorvastatin 20 mg in Achieving a Target Low Density Lipoprotein-Cholesterol Goal for Patients With Very High Risk. Korean Circ J 2011; 41 (3):149-53. PMID: 21519514

101. Foody JM, Brown WV, Zieve F et al. Safety and efficacy of ezetimibe/simvastatin combination versus atorvastatin alone in adults >/=65 years of age with hypercholesterolemia and with or at moderately high/high risk for coronary heart disease (the VYTELD study). Am J Cardiol 2010; 106(9):1255-63. PMID: 21029821

102. Okada K, Kimura K, Iwahashi N et al. Clinical usefulness of additional treatment with ezetimibe in patients with coronary artery disease on statin therapy. - From the viewpoint of cholesterol metabolism.-. Circ J 2011; 75 (10):2496-504. PMID: 21817821

103. Ostad MA, Eggeling S, Tschentscher P et al. Flow-mediated dilation in patients with coronary artery disease is enhanced by high dose atorvastatin compared to combined low dose atorvastatin and ezetimibe: results of the CEZAR study. Atherosclerosis 2009; 205(1):227-32. PMID: 19150064

104. Pesaro AE, Serrano CV Jr, Fernandes JL et al. Pleiotropic effects of ezetimibe/simvastatin vs. high dose simvastatin. Int J Cardiol 2012; 158(3):400-4. PMID: 21334753

105. Robinson JG, Ballantyne CM, Grundy SM et al. Lipid-altering efficacy and safety of ezetimibe/simvastatin versus atorvastatin in patients with hypercholesterolemia and the metabolic syndrome (from the VYMET study). Am J Cardiol 2009; 103(12):1694-702. PMID: 19539078

106. Tomassini JE, Mazzone T, Goldberg RB et al. Effect of ezetimibe/simvastatin compared with atorvastatin on lipoprotein subclasses in patients with type 2 diabetes and hypercholesterolaemia. Diabetes Obes Metab 2009; 11 (9):855-64. PMID: 19508464

107. Hamdan R, Hajj F, Kadry Z et al. Benefit and tolerability of the coadministration of ezetimibe and atorvastatin in acute coronary syndrome patients. J Med Liban 2011; 59(2):65-9. PMID: 21834489

108. Averna M, Zaninelli A, Le Grazie C, Gensini GF. Ezetimibe/simvastatin 10/20 mg versus simvastatin 40 mg in coronary heart disease patients. J Clin Lipidol 2010; 4(4):272-8. PMID: 21122660

109. Lee JH, Kang HJ, Kim HS, Sohn DW, Oh BH, Park YB. Effects of Ezetimibe/Simvastatin 10/20 mg vs. Atorvastatin 20 mg on Apolipoprotein B/Apolipoprotein A1 in Korean Patients with Type 2 Diabetes Mellitus: Results of a Randomized Controlled Trial. Am J Cardiovasc Drugs 2013. PMID: 23728830

110. Mohiuddin SM, Pepine CJ, Kelly MT et al. Efficacy and safety of ABT-335 (fenofibric acid) in combination with simvastatin in patients with mixed dyslipidemia: a phase 3, randomized, controlled study. Am Heart J 2009; 157(1):195-203. PMID: 19081418

111. Shah HD, Parikh KH, Chag MC et al. Beneficial effects of addition of fenofibrate to statin therapy in patients with acute coronary syndrome after percutaneous coronary interventions. World Heart Journal 2008; 1(1):69-77.

112. Barbi G et al. Effect of Pravastatin and Cholestyramine on Triglycerids-Rich Lipoprotein Particles and Lp(a) in Patients With Type II Hypercholesterolemia. 27. 1992:297-306. PMID:

113. Ismail F , Corder CN, Epstein S, Barbi G, Thomas S. Effects of pravastatin and cholestyramine on circulating levels of parathyroid hormone and vitamin D metabolites. Clin Ther 1990; 12(5):427-30. PMID: 2125243

114. Comparative efficacy and safety of pravastatin and cholestyramine alone and combined in patients with hypercholesterolemia. Pravastatin Multicenter Study Group II. Arch Intern Med 1993; 153(11):1321-9. PMID: 8507122

115. Knapp HH , Schrott H, Ma P et al. Efficacy and safety of combination simvastatin and colesevelam in patients with primary hypercholesterolemia. Am J Med 2001; 110(5):352-60. PMID: 11286949

116. Schrott HG, Stein EA, Dujovne CA et al. Enhanced low-density lipoprotein cholesterol reduction and cost-effectiveness by low-dose colestipol plus lovastatin combination therapy. Am J Cardiol 1995; 75(1):34-9. PMID: 7801861

117. Feldman T, Koren M, Insull W Jr et al. Treatment of high-risk patients with ezetimibe plus simvastatin co-administration versus simvastatin alone to attain National Cholesterol Education Program Adult Treatment Panel III low-density lipoprotein cholesterol goals. Am J Cardiol 2004; 93(12):1481-6. PMID: 15194017

118. Kerzner B, Corbelli J, Sharp S et al. Efficacy and safety of ezetimibe coadministered with lovastatin in primary hypercholesterolemia. Am J Cardiol 2003; 91(4):418-24. PMID: 12586255

119. Gardner SF, Schneider EF, Granberry MC, Carter IR. Combination therapy with low-dose lovastatin and niacin is as effective as higher-dose lovastatin. Pharmacotherapy 1996; 16(3):419-23. PMID: 8726600

120. Hunninghake DB, McGovern ME, Koren M et al. A dose-ranging study of a new, once-daily, dual-component drug product containing niacin extended-release and lovastatin. Clin Cardiol 2003; 26(3):112-8. PMID: 12685616

121. Insull W Jr, McGovern ME, Schrott H et al. Efficacy of extended-release niacin with lovastatin for hypercholesterolemia: assessing all reasonable doses with innovative surface graph analysis. Arch Intern Med 2004; 164(10):1121-7. PMID: 15159270

122. Kawagoe Y, Hattori Y, Nakano A et al. Comparative study between high-dose fluvastatin and low-dose fluvastatin and ezetimibe with regard to the effect on endothelial function in diabetic patients. Endocr J 2011; 58(3):171-5. PMID: 21304215

123. Farnier M, Steinmetz A, Retterstol K, Csaszar A. Fixed-dose combination fenofibrate/pravastatin 160/40 mg versus simvastatin 20 mg monotherapy in adults with type 2 diabetes and mixed hyperlipidemia uncontrolled with simvastatin 20 mg: a double-blind, randomized comparative study. Clin Ther 2011; 33(1):1-12. PMID: 21397769

124. Guyton JR, Goldberg RB, Mazzone T et al. Lipoprotein and apolipoprotein ratios in the VYTAL trial of ezetimibe/simvastatin compared with atorvastatin in type 2 diabetes. J Clin Lipidol 2008; 2(1):19-24. PMID: 21291711

125. Matsue Y, Matsumura A, Suzuki M, Hashimoto Y, Yoshida M. Differences in action of atorvastatin and ezetimibe in lowering low-density lipoprotein cholesterol and effect on endothelial function. Circ J 2013; 77(7):1791-8. PMID: 23603824

126. Bays HE, Davidson MH, Massaad R et al. Safety and efficacy of ezetimibe added on to rosuvastatin 5 or 10 mg versus up-titration of rosuvastatin in patients with hypercholesterolemia (the ACTE Study). Am J Cardiol 2011; 108(4):523-30. PMID: 21596364

127. Jones PH, Davidson MH, Kashyap ML et al. Efficacy and safety of ABT-335 (fenofibric acid) in combination with rosuvastatin in patients with mixed dyslipidemia: a phase 3 study. Atherosclerosis 2009; 204(1):208-15. PMID: 18996523

128. Capuzzi DM, Morgan JM, Weiss RJ, Chitra RR, Hutchinson HG, Cressman MD. Beneficial effects of rosuvastatin alone and in combination with extended-release niacin in patients with a combined hyperlipidemia and low high-density lipoprotein cholesterol levels. Am J Cardiol 2003; 91(11):1304-10. PMID: 12767421

129. Hayward RA, Krumholz HM.. Three reasons to abandon low-density lipoprotein targets: an open letter to the Adult Treatment Panel IV of the National Institutes of Health. Circ Cardiovasc Qual Outcomes. 2012; 5(1):2-5. PMID: 22253366

130. Stone NJ, Robinson J, Lichtenstein AH, et.al.. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013. PMID: 24239923

131. Haynes R, Jiang L, Hopewell JC et al. HPS2-THRIVE randomized placebo-controlled trial in 25 673 high-risk patients of ER niacin/laropiprant: Trial design, pre-specified muscle and liver outcomes, and reasons for stopping study treatment. Eur. Heart J. 2013; 34(17):1279-91.

132. Califf RM, Lokhnygina Y, Cannon CP, Stepanavage ME, et.al. An update on the IMProved reduction of outcomes: Vytorin Efficacy International Trial(IMPROVE-IT) design. Am Heart Journal 2010:

133. Guo J, Meng F, Ma N, Li C, et.al. Meta-analysis of safety of the coadministration of statin with fenofibrate in patients with combined hyperlipidemia. Am J Cardiol 2012; 110(9):1296-301.

134. Abramson BL, Benlian P, Hanson ME, Lin J, et. al. Response by sex to statin plus ezetimibe or statin monotherapy: a pooled analysis of 22,231hyperlipidemic patients. Lipids Health Dis. 2011; 10(146).:

135. Mikhailidis DP et. al. Comparative efficacy of the addition of ezetimibe to statin vsstatin titration in patients with hypercholesterolaemia: systematic review andmeta-analysis. Curr Med Res Opin. 27(6):1191-210. PMID:

136. Kashani A, Sallam T, Bheemreddy S, Mann DL et. al. Review ofside-effect profile of combination ezetimibe and statin therapy in randomizedclinical trials. Am J Cardiol. 2008; 101(11):1606-12

137. Mikhailidis DP SGBCDGCAL. Meta-analysis of the cholesterol-lowering effect of ezetimibe added to ongoingstatin therapy. Curr Med Res Opin 23(8):2009-26

138. Caspard H, Chan AK, Walker AM. Compliance with a statin treatment in ausual-care setting: retrospective database analysis over 3 years after treatment initiation in health maintenance organization enrollees with dyslipidemia. ClinTher. 2005; 27(10):1639-46. PMID: PMID: 16330301

139. Rees K, Dyakova M, Ward K, Thorogood M, Brunner E. Dietary advice for reducing cardiovascular risk. Cochrane Database Syst Rev. 2013 2013. PMID: 23543514

140. Hooper L, Summerbell CD, Thompson R, et. al. Reduced or modified dietary fat for preventing cardiovascular disease. Cochrane Database Syst Rev. 2012 PMID: 22592684

141. SEARCH Collaborative Group, Link E, Parish S, Armitage J, Bowman L, Heath S,Matsuda F, Gut I, Lathrop M, Collins R.. SLCO1B1 variants and statin-inducedmyopathy--a genomewide study. N Engl J Med 2008; 359(8):789-99. PMID: 18650507

142. Krauss RM, Mangravite LM, Smith JD, et. al. Variation in the 3-hydroxyl-3-methylglutaryl coenzyme a reductase geneis associated with racial differences in low-density lipoprotein cholesterolresponse to simvastatin treatment. Circulation 2008; 117(12):1537-44.

Appendix A. Acronyms and Abbreviations

ACC	American College of Cardiology
ACCF	American College of Cardiology Foundation
ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACS	Acute coronary syndrome
ADA	American Diabetes Association
AE	Adverse events
AHA	American Heart Association
AHRQ	Agency for Healthcare Research and Quality
AIM-HIGH	Atherothrombosis Intervention in Metabolic Syndrome with Low HDL Cholesterol/High Triglyceride and Impact on Global Health Outcomes
AKI	Acute kidney injury
ALT	Alanine transaminase
ARBITER-6 HALTS	Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6–HDL and LDL Treatment Strategies in Atherosclerosis
AST	Aspartate transaminase
ATP	Adult Treatment Panel
ATV	Atorvastatin
BAS	Bile acid sequestrants
CAD	Coronary artery disease
CENTRAL	Cochrane Central Register of Controlled Trials
CHD	Coronary heart disease
CI	Confidence interval
CIMT	Carotid intima-media thickness
CPK	Creatinine phospokinase
CVD	Cardiovascular disease
DHA	Docosahexaenoic acid
DM	Diabetes mellitus
ENHANCE	The Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression
EPA	Eicosapentaenoic acid
FDA	U.S. Food and Drug Administration
FH	Familial hypercholesterolemia
HDL-c	High-density lipoprotein
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A
HSP-2 THRIVE	Heart Protection Study 2 Treatment of HDL to Reduce the Incidence of Vascular Events
IMPROVE-IT	Improved Reduction of Outcomes: Vytorin Efficacy International
LDL-c	Low-density lipoprotein
LOV	Lovastatin
LS	Least square
MI	Myocardial infarction

NA	Not applicable
NHBLI	The National Heart, Lung, and Blood Institute
NCEP	National Cholesterol Education Program
N-ER	Niacin- extended release
NPC1L1	Niemann-Pick C1-like protein
NR	Not reported
NRS	Non-randomized studies
NS	Not significant
OIS	optimal information size
PICOS	Population intervention comparison outcome setting
PMSG II	Pravastatin Multicenter Study Group II.
RCT	Randomized controlled study
RSV	Rosuvasttain
SAE	Serious adverse events
SD	Standard deviation
SE	Standard error
SIP	Scientific information packet
SMV	Simvastatin
SOE	Strength of evidence
SRDR	Systematic Review Data Repository
TC	Total cholesterol
TIA	Transient ischemic attack
UA	Unstable angina
ULN	Upper normal limit

Appendix B. Detailed Search Strategies

PubMed

“Hydroxymethylglutaryl-CoA Reductase Inhibitors” [mh] OR “Heptanoic Acids” [mh] OR “Heptanoic Acids” [tiab] OR statin*[tiab] OR “reductase inhibitor”[tiab] OR Simvastatin [mh] OR Simvastatin [tiab] OR Atorvastatin [nm] OR Atorvastatin [tiab] OR Rosuvastatin [nm] OR Rosuvastatin [tiab] OR Pravastatin [mh] OR Pravastatin [tiab] OR Lovastatin [mh] OR Lovastatin [tiab] OR Fluvastatin [nm] OR Fluvastatin [tiab] OR Pitavastatin[nm] OR Pitavastatin[tiab]

AND

("fatty acids, omega-3"[MeSH Terms] OR "omega 3" [tiab] OR “fatty acids” [tiab] OR "fatty acids, essential"[MeSH Terms] OR "dietary fats, unsaturated"[MeSH Terms] OR linolenic acids [tiab] OR "fish oils"[MeSH Terms] OR “fish oils” [tiab] OR “alpha linolenic acid” [tiab] OR linolenate[tiab] OR "nervonic acid"[nm]OR “nervonic acid”[tiab] OR timnodonic acid[tiab] OR "diet, mediterranean"[MeSH Terms] OR (Mediterranean[tiab] AND diet[tiab]) OR "flax"[MeSH Terms] OR "brassica rapa"[MeSH Terms] OR "soybeans"[MeSH Terms] OR "juglans"[MeSH Terms] OR ((Flax[tiab] OR flaxseed [tiab] OR linseed [tiab] OR rapeseed [tiab] OR canola [tiab] OR soybean [tiab] OR walnut [tiab]) AND Oil[tiab]) OR "cod liver oil"[MeSH Terms] OR “cod liver oil”[tiab] OR salmon[MH] OR salmon[tiab]OR "perciformes"[MeSH Terms] OR mackerel[tiab] or "tuna"[MeSH Terms] or tuna[tiab] or "flounder"[MeSH Terms] or halibut[tiab] or "seals, earless"[MeSH Terms] or seal[tiab] or "seaweed"[MeSH Terms] or seaweed [tiab] OR "anticholesteremic agents"[MeSH Terms] OR anticholesteremics [tiab] OR "bile acids and salts"[MeSH Terms] OR “bile acids”[tiab] OR (bile[tiab] AND resin*[tiab]) OR “bile acid sequestrant”[tiab] OR "cholestyramine resin"[MeSH Terms] OR cholestyramine [tiab] OR colestyramin [tiab] OR "colesevelam"[Supplementary Concept] OR colesevelam[tiab] OR "colestipol"[MeSH Terms] OR Colestipol [tiab] OR colestilan[tiab] OR "ezetimibe"[Supplementary Concept] OR ezetimibe[tiab] OR (cholesterol*[tiab] AND inhibitors*[tiab]) OR "fibric acids"[MeSH Terms] OR fibrates [tiab] OR fibric acid [tiab] OR Gemfibrozil [tiab] OR fenofibrate [tiab] OR niacin [MH] OR niacin [tiab] OR nicotinic acid[MH] OR nicotinic acid[tiab] OR "drug therapy, combination"[MeSH Terms] OR (combination[tiab] AND therapy[tiab]) OR"add-on therapy" [ti])

AND

"cardiovascular diseases"[MeSH Terms]OR “cardiovascular disease” [tiab] OR "cardiovascular diseases"[tiab] OR “myocardial infarction” [tiab] OR strokes [tiab] OR “heart failure”[tiab] OR “arrhythmia”[tiab] OR “heart valve disease”[tiab] OR hypertension [tiab] or coronary [tiab] OR angina [tiab] OR “cerebrovascular accident” [tiab] OR “Hypercholesterolemia” [mh] OR “Hypercholesterolemia” [tiab] OR hypercholesterolaemia [tiab] OR “Hyperlipidemias”[mh] OR “Hyperlipidemias”[tiab] OR hyperlipidaemia [tiab] OR “transient ischemic attack” [tiab] OR “transient ischaemic attack” [tiab] OR “TIA”[tiab] OR Dyslipidemias[mh] OR Dyslipidemias[tiab] OR Dyslipidemia[tiab]

AND

(randomized controlled trial[pt] OR controlled clinical trial [pt] or randomized controlled trials[mh] or random allocation[mh] or double-blind method[mh] or single-blind method[mh] OR clinical trial[pt] or clinical trials[mh] or (“clinical trial”[tw]) OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind* [tw])) OR (“latin square”[tw]) OR placebos[mh] OR placebo*[tw] OR rando*[tw] OR research design[mh:noexp]) Not (animal[mh] Not human[mh])

Appendix C. Screening and Data Abstraction Forms

Title-Abstract Screening Form

Refid: 12, Skateboards: Are they really perilous? A retrospective study from a district hospital.
Rethnam U, Yesupalan RS, Sinha A.

Submit Form and go to or Skip to Next

Does this article POTENTIALLY apply to ANY of the key questions?

- No

  NO, this article DOES NOT apply to any of the Key Questions (check only one reason)

  - Study published before 2008
  - Not conducted in humans
  - No original data (systematic reviews, meta-analysis, editorial, commentary)
  - Not in English and not able to determine eligibility criteria
  - No full report (e.g. conference or meeting abstract)
  - Not an RCT or non-randomized that is extension of RCT that lasts >24 weeks
  - Drug is not available in the U.S./ non-approved(e.g. Investigational fibrate)
  - Not relevant to key questions
  - Other: Please specify

  Clear Response

- Yes-Include article for full text screening
- Unclear-No abstract or cannot tell from abstract alone --- get it for full-text screen

Flag excluded articles:

- Pull for hand searching – review that applies to one of the questions and likely to contain relevant studies
- Pull for citation for use in report (i.e., for background)

Clear Response

Please click here to see the list of included and excluded drugs

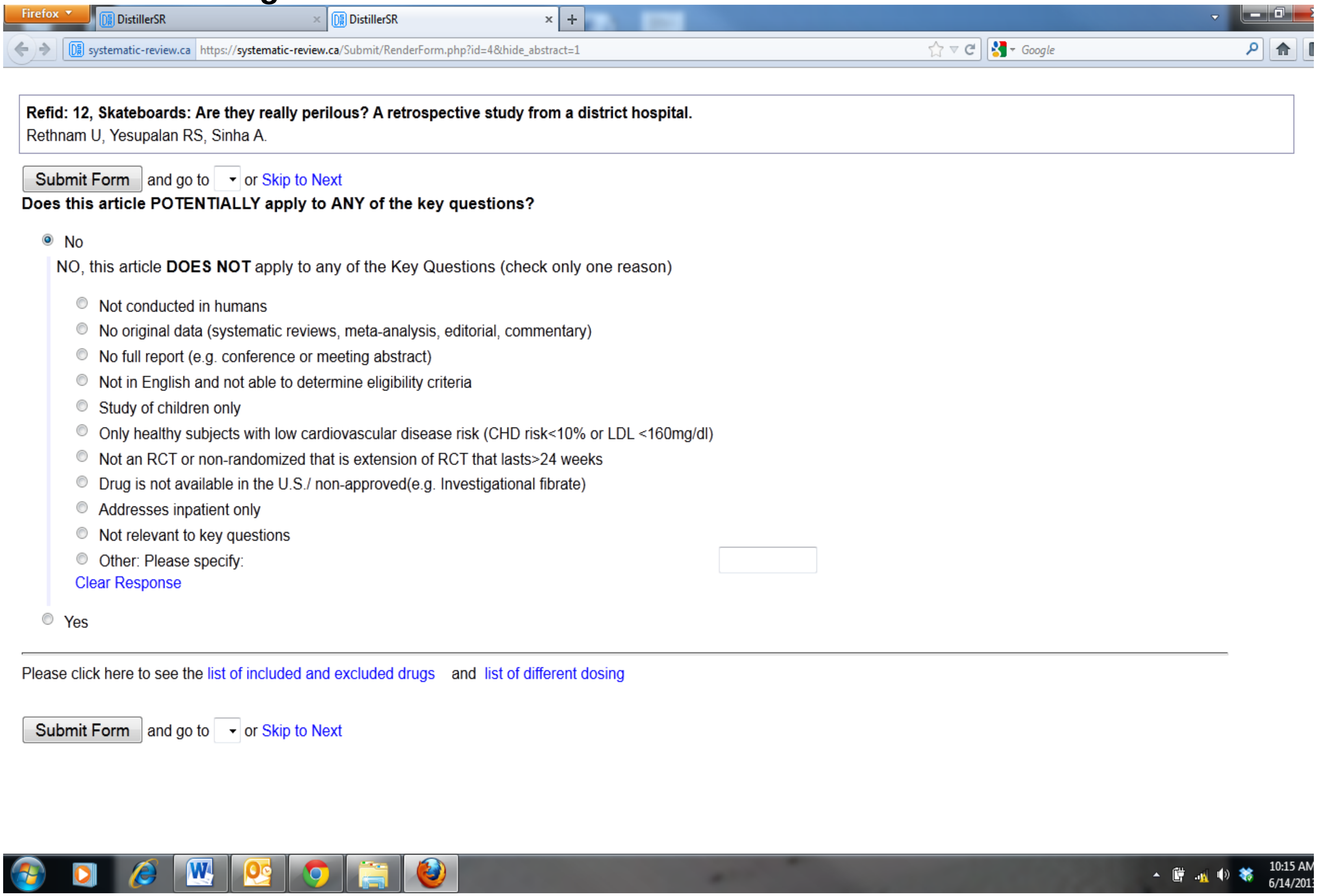
Key Questions

KQ 1:For patients who require intensive lipid-modifying therapy, what are the comparative long-term benefits and rates of serious adverse events of co-administration of different lipid-modifying agents (i.e., a statin plus another lipid-modifying agent) compared with higher dose statin monotherapy?

KQ 2:Do these regimens differ in reaching LDL targets (or other surrogate markers), short-term side effects, tolerability, and/or adherence?

KQ 3:Compared with higher dose statins and to one another, do combination regimens differ in benefits and harms within subgroups of patients?

Article Screening Form – Exclusion



Refid: 12, Skateboards: Are they really perilous? A retrospective study from a district hospital.
Rethnam U, Yesupalan RS, Sinha A.

Submit Form and go to or Skip to Next

Does this article POTENTIALLY apply to ANY of the key questions?

- (•) No

NO, this article **DOES NOT** apply to any of the Key Questions (check only one reason)

- ( ) Not conducted in humans
- ( ) No original data (systematic reviews, meta-analysis, editorial, commentary)
- ( ) No full report (e.g. conference or meeting abstract)
- ( ) Not in English and not able to determine eligibility criteria
- ( ) Study of children only
- ( ) Only healthy subjects with low cardiovascular disease risk (CHD risk<10% or LDL <160mg/dl)
- ( ) Not an RCT or non-randomized that is extension of RCT that lasts>24 weeks
- ( ) Drug is not available in the U.S./ non-approved(e.g. Investigational fibrate)
- ( ) Addresses inpatient only
- ( ) Not relevant to key questions
- ( ) Other: Please specify:

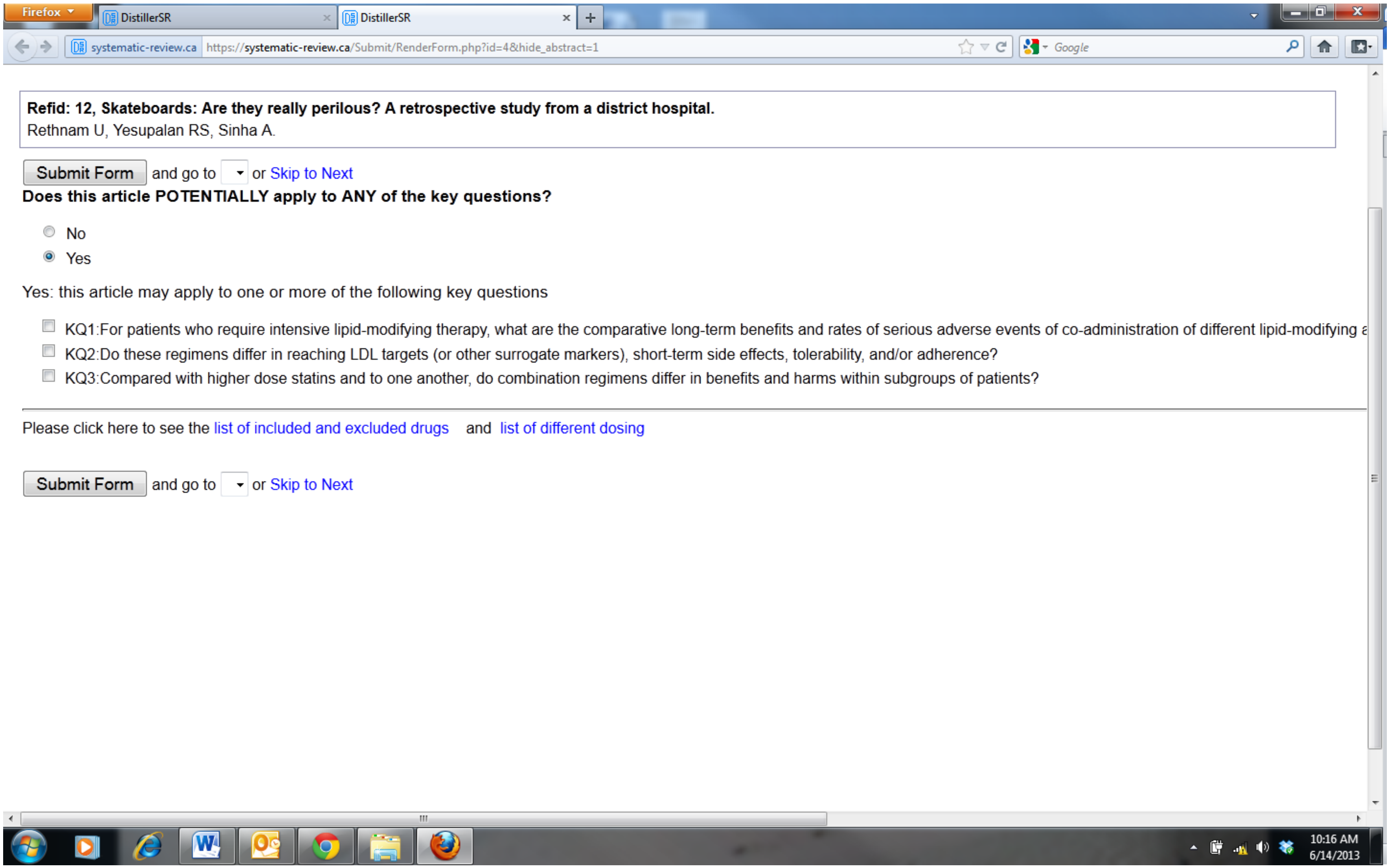
Clear Response

- ( ) Yes

Please click here to see the list of included and excluded drugs and list of different dosing

Submit Form and go to or Skip to Next

Article Screening Form – Inclusion



Refid: 12, Skateboards: Are they really perilous? A retrospective study from a district hospital.
Rethnam U, Yesupalan RS, Sinha A.

Submit Form and go to or Skip to Next

Does this article POTENTIALLY apply to ANY of the key questions?

- No
- Yes

Yes: this article may apply to one or more of the following key questions

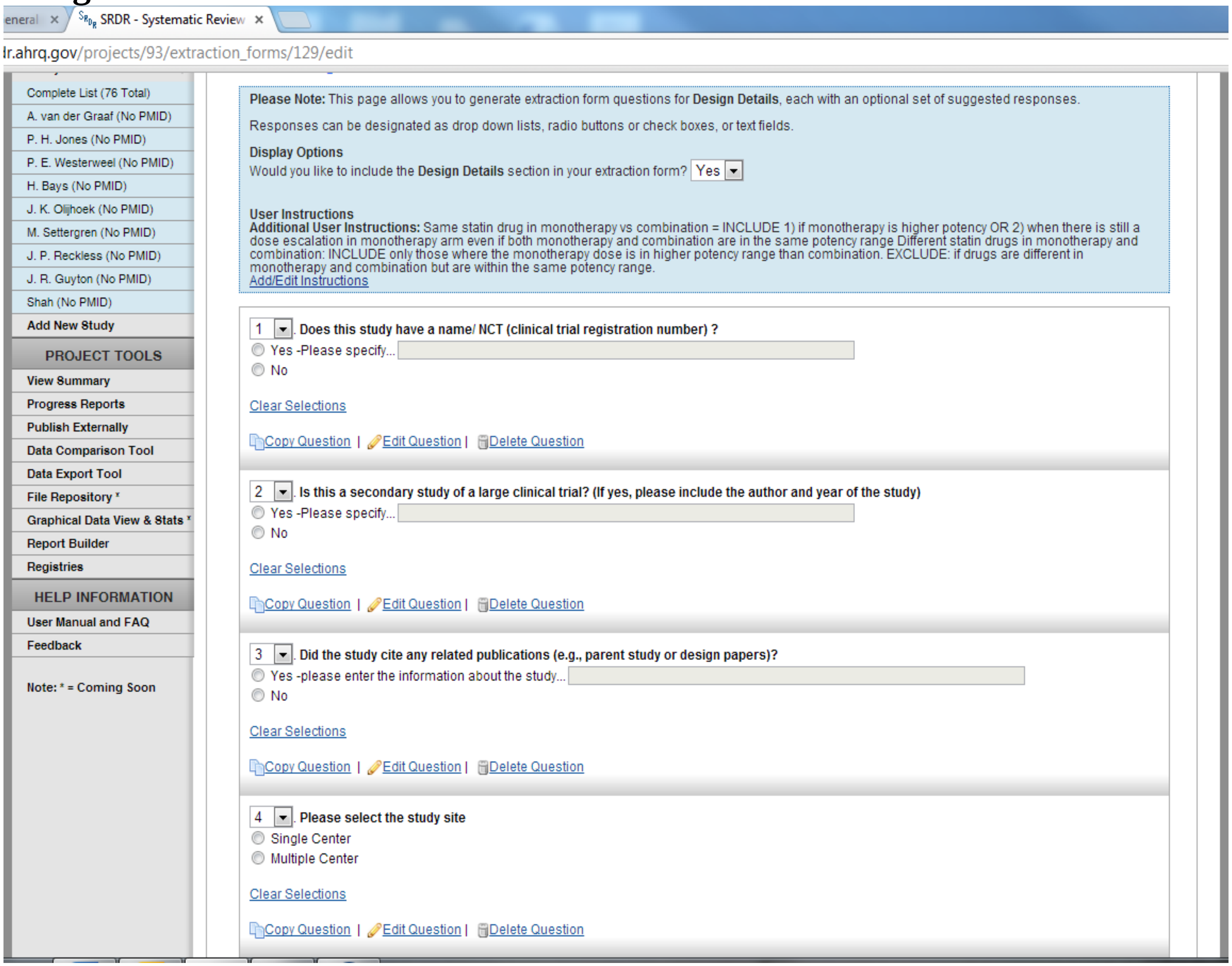
- KQ1:For patients who require intensive lipid-modifying therapy, what are the comparative long-term benefits and rates of serious adverse events of co-administration of different lipid-modifying a
- KQ2:Do these regimens differ in reaching LDL targets (or other surrogate markers), short-term side effects, tolerability, and/or adherence?
- KQ3:Compared with higher dose statins and to one another, do combination regimens differ in benefits and harms within subgroups of patients?

Please click here to see the list of included and excluded drugs and list of different dosing

Submit Form and go to or Skip to Next

SRDR – Data Abstraction Forms

Design Form



atic Review ×

xtraction_forms/129/edit

5 . **Please select the study location - check all that apply**

- [ ] North America
- [ ] Centeral South America
- [ ] Euorpe
- [ ] Africa
- [ ] Asia
- [ ] MiddleEast
- [ ] Australia
- [ ] Not reported

Copy Question | Edit Question | Delete Question

6 . **What study design was used?**

- ( ) RCT
- ( ) NRS
- ( ) FDA report/Grey Literature

Clear Selections

Copy Question | Edit Question | Delete Question

7 . **If a randomized controlled trial, select type.**

- [ ] Parallel arms
- [ ] Factorial design
- [ ] Crossover design
- [ ] Other (specify): ...

Copy Question | Edit Question | Delete Question

8 . **If it applies (e.g. crossover), was there a washout period between therapies?**

- ( ) Yes
- ( ) No
- ( ) Not reported
- ( ) Not Applicable
- ( ) Other(specify)...

Clear Selections

Copy Question | Edit Question | Delete Question

129/edit

9 . Please specify the inclusion criteria. Any exclusion criteria should be entered as inclusion criteria (e.g., if the study only excluded females, then the inclusion criteria would be males).

- [ ] Age...
- [ ] Female...
- [ ] Race/Ethinicity...
- [ ] Patients with Cardiovascular disease...
- [ ] Diabetic patients...
- [ ] Other1 inclusion criteria...
- [ ] Other 2 inclusion criteria...
- [ ] Other 3 inclusion criteria...
- [ ] Other 4 inclusion criteria...

Copy Question | Edit Question | Delete Question

10 . Did this study include the patients with prior statin use "EVER" or "PRIOR TO TRIAL ENTRY"

- Yes -Prior statin use ever
- Yes-Prior to trial entry
- Not
- Not reported

Clear Selections

Copy Question | Edit Question | Delete Question

11 . Was there a period of follow-up before patients were randomized aka "run-in period"? If yes what was the duration of the run-in period? (Enter number and then select units)

	"Run-in
"Duration"	
"Unit"	Select...

Other
(please specify):

Please enter "NR" for duration if study did not report the run-in period

Copy Question | Edit Question | Delete Question

12 . What was the duration of treatment from randomization?

	"treatment
"Duration"	
"Unit"	Select...

Please enter "NR" for duration if study did not report the duration of treatment

Copy Question | Edit Question | Delete Question

ms/129/edit

13 . **Please select the intensification of Statin Monotherapy Agent(s)**

	1	2	3	4
Statin	Select...	Select...	Select...	Select...

Copy Question | Edit Question | Delete Question

14 . **Please select the Combination Therapy Agent(s)**

	1	2	3	4
"Statin"	Select...	Select...	Select...	Select...
"Other'	Select...	Select...	Select...	Select...
'Prepackaged	Select...	Select...	Select...	Select...

Copy Question | Edit Question | Delete Question

15 . **Which subgroups analyses were conducted? (Select all that apply)**

- [ ] All elderly - patients older than 80
- [ ] High CVD risk elderly - patients older than 80
- [ ] All women
- [ ] High CVD risk women
- [ ] All race - African-American, Asian and Hispanic
- [ ] High CVD risk race
- [ ] Patients with diabetes (type 1 or 2)
- [ ] Patients with established vascular disease (peripheral vascular disease, cerebrovascular disease, and/or CAD)
- [ ] Patients with established coronary heart disease (CAD, MI, ACS, unstable, angina, CABG, PCI)
- [ ] Patients with established cerebrovascular disease (stroke, TIA)
- [ ] Patients with baseline LDL>=190mg/dL
- [ ] No subgroup analyses were conducted

Copy Question | Edit Question | Delete Question

16 . **Was there industry support (funding or drug given) or government support for the study? (Check all that apply)**

- [ ] Yes, industry support
- [ ] Yes, government support
- [ ] Yes, other support
- [ ] No
- [ ] Not reported

Copy Question | Edit Question | Delete Question

17. Did the study author(s) disclose any financial relationship with pharmaceuticals OR were the study authors employee of pharmaceutical company (ies)

- [ ] Yes-Financial relationship with pharmaceuticals
- [ ] Yes-Employee of pharmaceutical company
- [ ] No
- [ ] Not reported

Copy Question | Edit Question | Delete Question

18. Other comments:

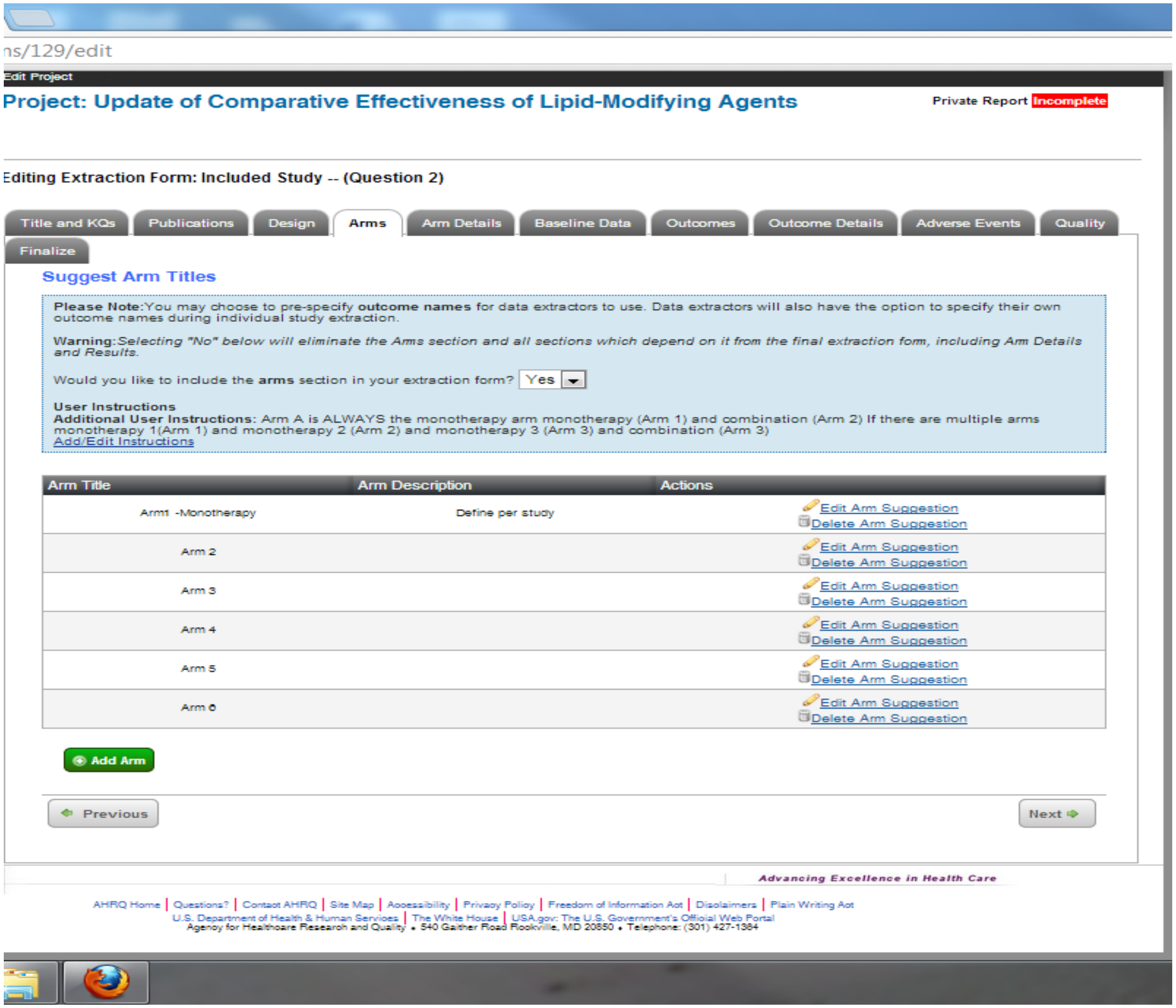
Copy Question | Edit Question | Delete Question

Add a New Design Detail

Advancing Excellence in Health Care

AHRQ Home | Questions? | Contact AHRQ | Site Map | Accessibility | Privacy Policy | Freedom of Information Act | Disclaimers | Plain Writing Act

Arms



ns/129/edit

Edit Project

Project: Update of Comparative Effectiveness of Lipid-Modifying Agents

Private Report **Incomplete**

Editing Extraction Form: Included Study -- (Question 2)

Title and KQs | Publications | Design | **Arms** | Arm Details | Baseline Data | Outcomes | Outcome Details | Adverse Events | Quality | Finalize

Suggest Arm Titles

Please Note: You may choose to pre-specify **outcome names** for data extractors to use. Data extractors will also have the option to specify their own outcome names during individual study extraction.

Warning: *Selecting "No" below will eliminate the Arms section and all sections which depend on it from the final extraction form, including Arm Details and Results.*

Would you like to include the **arms** section in your extraction form? Yes

User Instructions
Additional User Instructions: Arm A is ALWAYS the monotherapy arm monotherapy (Arm 1) and combination (Arm 2) If there are multiple arms monotherapy 1(Arm 1) and monotherapy 2 (Arm 2) and monotherapy 3 (Arm 3) and combination (Arm 3)
Add/Edit Instructions

Arm Title	Arm Description	Actions
Arm1 -Monotherapy	Define per study	Edit Arm Suggestion Delete Arm Suggestion
Arm 2		Edit Arm Suggestion Delete Arm Suggestion
Arm 3		Edit Arm Suggestion Delete Arm Suggestion
Arm 4		Edit Arm Suggestion Delete Arm Suggestion
Arm 5		Edit Arm Suggestion Delete Arm Suggestion
Arm 6		Edit Arm Suggestion Delete Arm Suggestion

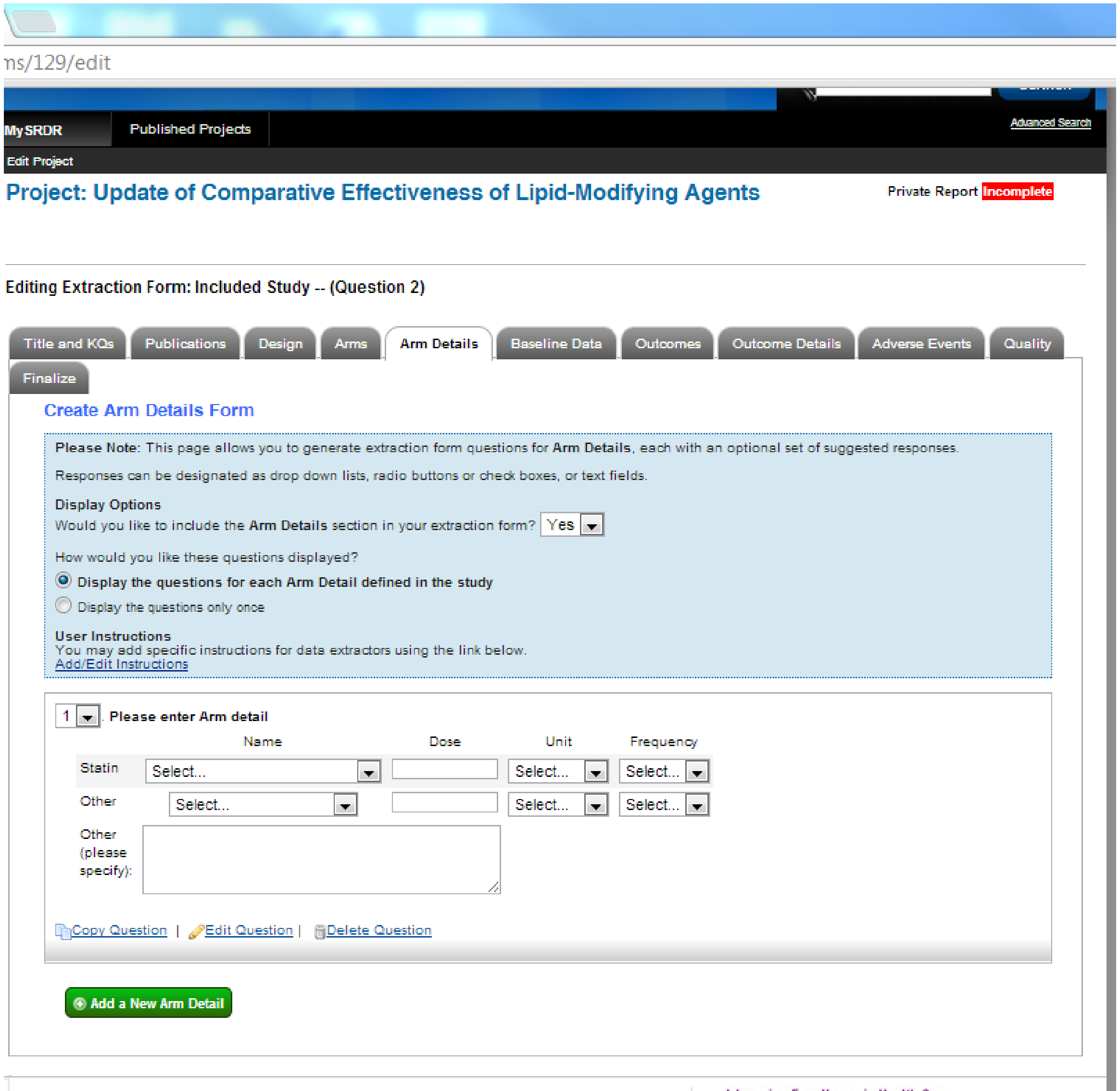
Add Arm

Previous | Next

Advancing Excellence in Health Care

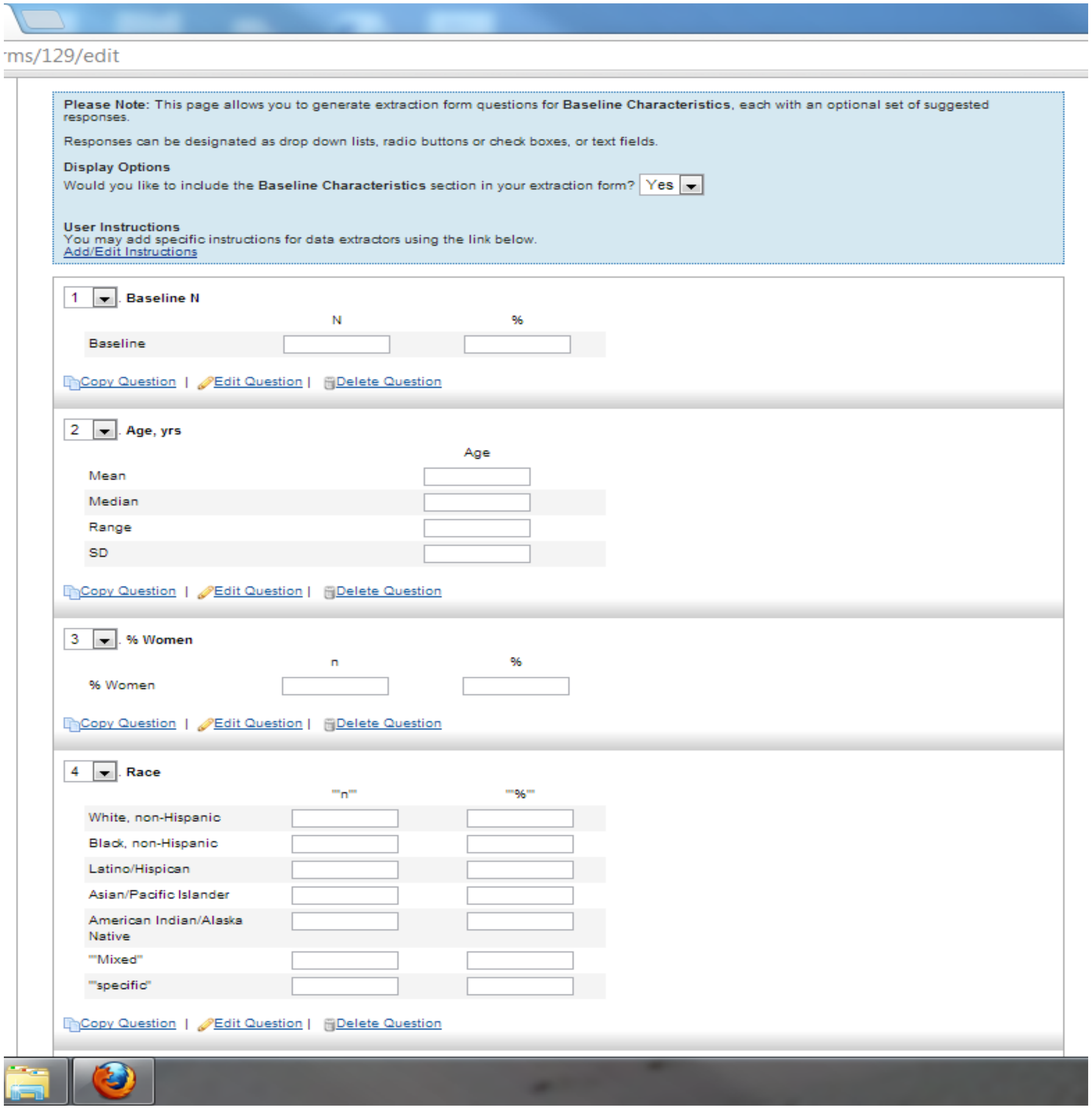
AHRQ Home | Questions? | Contact AHRQ | Site Map | Accessibility | Privacy Policy | Freedom of Information Act | Disclaimers | Plain Writing Act
U.S. Department of Health & Human Services | The White House | USA.gov: The U.S. Government's Official Web Portal
Agency for Healthcare Research and Quality • 540 Gaither Road Rockville, MD 20850 • Telephone: (301) 427-1364

Arm Details



ns/129/edit
Advanced Search
My SRDR
Published Projects
Edit Project
Project: Update of Comparative Effectiveness of Lipid-Modifying Agents
Private Report Incomplete
Editing Extraction Form: Included Study -- (Question 2)
Title and KQs
Publications
Design
Arms
Arm Details
Baseline Data
Outcomes
Outcome Details
Adverse Events
Quality
Finalize
Create Arm Details Form
Please Note: This page allows you to generate extraction form questions for Arm Details, each with an optional set of suggested responses.
Responses can be designated as drop down lists, radio buttons or check boxes, or text fields.
Display Options
Would you like to include the Arm Details section in your extraction form? Yes
How would you like these questions displayed?
Display the questions for each Arm Detail defined in the study
Display the questions only once
User Instructions
You may add specific instructions for data extractors using the link below.
Add/Edit Instructions
1. Please enter Arm detail
Name
Dose
Unit
Frequency
Statin
Select...
Select...
Select...
Other
Select...
Select...
Select...
Other (please specify):
Copy Question | Edit Question | Delete Question
Add a New Arm Detail
Advancing Excellence in Health Care

Baseline Data Characteristics



ms/129/edit

Please Note: This page allows you to generate extraction form questions for **Baseline Characteristics**, each with an optional set of suggested responses.

Responses can be designated as drop down lists, radio buttons or check boxes, or text fields.

Display Options
Would you like to include the **Baseline Characteristics** section in your extraction form? Yes

User Instructions
You may add specific instructions for data extractors using the link below.
Add/Edit Instructions

1 . **Baseline N**

	N	%
Baseline		

Copy Question | Edit Question | Delete Question

2 . **Age, yrs**

	Age
Mean	
Median	
Range	
SD	

Copy Question | Edit Question | Delete Question

3 . **% Women**

	n	%
% Women		

Copy Question | Edit Question | Delete Question

4 . **Race**

	""n""	""%""
White, non-Hispanic		
Black, non-Hispanic		
Latino/Hispican		
Asian/Pacific Islander		
American Indian/Alaska Native		
""Mixed"		
""specific"		

Copy Question | Edit Question | Delete Question

6 . **Patients with history of MI**

	'n'	'%'
Patients with history of MI		

Copy Question | Edit Question | Delete Question

7 . **Patients with history of Stroke**

	'n'	'%'
Patients with history of Stroke		

Copy Question | Edit Question | Delete Question

8 . **Patients with history of revascularization**

	'n'	'%'
Patients with history of revascularization		

Copy Question | Edit Question | Delete Question

9 . **Diabetic patients**

	"n"	"%"
Diabetic patients		

Copy Question | Edit Question | Delete Question

10 . **Baseline LDL**

	Mean	SD	SE
Baseline-LDL			

Copy Question | Edit Question | Delete Question

9 . **Diabetic patients**

	"n"	"%"
Diabetic patients		

Copy Question | Edit Question | Delete Question

10 . **Baseline LDL**

	Mean	SD	SE
Baseline-LDL			

Copy Question | Edit Question | Delete Question

11 . **CHD risk score**

	Mean	SD	SE
CHD risk score			

Copy Question | Edit Question | Delete Question

12 . **If any of above characteristics differs by group, please describe**

Copy Question | Edit Question | Delete Question

13 . **Other comments:**

Copy Question | Edit Question | Delete Question

Results

edit

Comments (2) | Post/View

Step 1. Choose the outcome and population to enter data for:

--- Continuous ---

OR Hide Existing Data Entries

Existing Results Entries

Outcome: Surrogate outcome -Participants attaining ATP III LDL-c targets   Population: All Participants   Edit | Remove

Time Point	Measure	Arm1 -Monotherapy	Arm 2
0 weeks	N Enrolled	111	108
	Counts	0	0
	Standard Deviation	NR	NR

Outcome: Surrogate outcome -Participants attaining ATP III LDL-c targets   Population: All Participants   Edit | Remove

Time Point	Measure	Arm1 -Monotherapy	Arm 2
6 weeks	N Enrolled	49.5 [1]	67.6 [2]
	Counts	NR	NR
	Standard Deviation	NR	NR

Footnotes

1. LDL less than 100
2. LDL less than 100

Outcome: Surrogate outcome -LDL-c   Population: All Participants   Edit | Remove

Time Point	Measure	Arm1 -Monotherapy	Arm 2
0 weeks	N Analyzed	111	108
	Mean	179	180

Outcome: Surrogate outcome -LDL-c   Population: All Participants   Edit | Remove

Time Point	Measure	Arm1 -Monotherapy	Arm 2
6 weeks	N Analyzed	111	108
	Mean	44.40% reduction	56.10% reduction

Section Status: Complete

Mark Section Incomplete

Previous   Next

Appendix D. List of Excluded Articles

No Original Data

E. M. Roth, R. S. Rosenson, P. H. Jones, M. H. Davidson, M. T. Kelly, C. M. Setze, A. Lele and K. Thakker.Attainment of goal/desirable lipid levels in patients with mixed dyslipidemia after 12 weeks of treatment with fenofibric acid and rosuvastatin combination therapy: A pooled analysis of controlled studies. J Clin Lipidol 2012: 534-44

L. Ma, C. M. Ballantyne, J. W. Belmont, A. Keinan and A. Brautbar.Interaction between SNPs in the RXRA and near ANGPTL3 gene region inhibits apoB reduction after statin-fenofibric acid therapy in individuals with mixed dyslipidemia. J Lipid Res 2012: 2425-8

A. D. Hingorani, R. Sofat, R. W. Morris, P. Whincup, G. D. Lowe, J. Mindell, N. Sattar, J. P. Casas and T. Shah.Is it important to measure or reduce C-reactive protein in people at risk of cardiovascular disease?. Eur Heart J 2012: 2258-64

W. Elmallah and R. A. Krasuski.Therapy and clinical trials. Curr Opin Lipidol 2011: 512-3

C. M. Ballantyne, M. H. Davidson, C. M. Setze and M. T. Kelly.Effects of combination therapy with rosuvastatin and fenofibric acid in patients with mixed dyslipidemia and high-sensitivity C-reactive protein (>/= 2 mg/L). cmb@bcm.tmc.edu. J Clin Lipidol 2011: 401-7

M. Averna, L. Missault, H. Vaverkova, M. Farnier, M. Viigimaa, Q. Dong, A. Shah, A. O. Johnson-Levonas, W. Taggart and P. Brudi.Lipid-altering efficacy of switching to ezetimibe/simvastatin 10/20 mg versus rosuvastatin 10 mg in high-risk patients with and without metabolic syndrome. Diab Vasc Dis Res 2011: 262-70

H. Takagi, M. Matsui and T. Umemoto.High-density lipoprotein-dependent effects of statins on the risk of coronary heart disease deaths and events. Int J Cardiol 2011: 377-9

P. S. Sever, N. R. Poulter, C. L. Chang, A. Hingorani, S. A. Thom, A. D. Hughes, P. Welsh and N. Sattar.Evaluation of C-reactive protein prior to and on-treatment as a predictor of benefit from atorvastatin: observations from the Anglo-Scandinavian Cardiac Outcomes Trial. Eur Heart J 2012: 486-94

I. Idris, H. Tate, A. Ahmad and T. McCormack.Concordance between plasma apolipoprotein B levels and cholesterol indices among patients receiving statins and nonstatin treatment: Post-hoc analyses from the U.K. InPractice study. J Clin Lipidol 2011: 316-23

M. Farnier, W. Taggart, Q. Dong, J. Lin, A. Shah and P. Brudi.Influence of simvastatin, fenofibrate and/or ezetimibe on correlation of low-density lipoprotein and nonhigh-density lipoprotein cholesterol with apolipoprotein B in mixed dyslipidemic patients. J Clin Lipidol 2011: 179-87

J. Spertus.Clinical trial subgroups: challenges and opportunities in describing the benefits of therapy. Circ Cardiovasc Qual Outcomes 2011: 266-7

S. M. Mohiuddin, K. M. Thakker, C. M. Setze and M. T. Kelly.Evaluating optimal lipid levels in patients with mixed dyslipidemia following short- and long-term treatment with fenofibric acid and statin combination therapy: a post hoc analysis. Curr Med Res Opin 2011: 1067-78

.ASCOT analysis with atorvastatin shows limits of CRP as indicator of cardiovascular risk. Cardiovasc J Afr 2011: 51

A. Yip and R. A. Hegele.Lipid modification in the elderly using the combination of a statin and a cholesterol absorption inhibitor. Expert Opin Pharmacother 2011: 675-8

A. C. Goldberg, V. Bittner, C. J. Pepine, M. T. Kelly, K. Thakker, C. M. Setze, A. Lele and D. J. Sleep.Efficacy of fenofibric acid plus statins on multiple lipid parameters and its safety in women with mixed dyslipidemia. Am J Cardiol 2011: 898-905

R. S. Rosenson, D. M. Carlson, M. T. Kelly, C. M. Setze, B. Hirshberg, J. C. Stolzenbach and L. A. Williams.Achievement of lipid targets with the combination of rosuvastatin and fenofibric Acid in patients with type 2 diabetes mellitus. Cardiovasc Drugs Ther 2011: 47-57

L. H. Breimer and D. P. Mikhailidis.Trials by independent expert bodies. Arch Intern Med 2010: 2042; author reply 2043-4

H. Bays, S. Conard, L. A. Leiter, S. Bird, E. Jensen, M. E. Hanson, A. Shah and A. M. Tershakovec.Are post-treatment low-density lipoprotein subclass pattern analyses potentially misleading?. Lipids Health Dis 2010: 136

M. Vega de Ceniga.Comments regarding 'A randomised placebo-controlled double-blind trial to evaluate lipid-lowering pharmacotherapy on proteolysis and inflammation in abdominal aortic aneurysms'. Eur J Vasc Endovasc Surg 2011: 36-7

C. J. Pepine, T. A. Jacobson, D. M. Carlson, M. T. Kelly, C. M. Setze, A. Gold, J. C. Stolzenbach and L. A. Williams.Combination rosuvastatin plus fenofibric acid in a cohort of patients 65 years or older with mixed dyslipidemia: subanalysis of two randomized, controlled studies. Clin Cardiol 2010: 609-19

L. A. Leiter, H. Bays, S. Conard, J. Lin, M. E. Hanson, A. Shah and A. M. Tershakovec.Attainment of Canadian and European guidelines' lipid targets with atorvastatin plus ezetimibe vs. doubling the dose of atorvastatin. Int J Clin Pract 2010: 1765-72

H. E. Bays, S. E. Conard, L. A. Leiter, S. R. Bird, R. S. Lowe and A. M. Tershakovec.Influence of age, gender, and race on the efficacy of adding ezetimibe to atorvastatin vs. atorvastatin up-titration in patients at moderately high or high risk for coronary heart disease. Int J Cardiol 2011: 141-7

A. M. Tonkin and L. Chen.Effects of combination lipid therapy in the management of patients with type 2 diabetes mellitus in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Circulation 2010: 850-2

A. Tomillero and M. A. Moral.Gateways to clinical trials. Methods Find Exp Clin Pharmacol 2010: 331-88

C. M. Rotella, A. Zaninelli, C. Le Grazie, M. E. Hanson and G. F. Gensini.Ezetimibe/simvastatin vs simvastatin in coronary heart disease patients with or without diabetes. Lipids Health Dis 2010: 80

H. E. Bays, E. M. Roth, J. M. McKenney, M. T. Kelly, K. M. Thakker, C. M. Setze, K. Obermeyer and D. J. Sleep.The effects of fenofibric acid alone and with statins on the prevalence of metabolic syndrome and its diagnostic components in patients with mixed dyslipidemia. Diabetes Care 2010: 2113-6

J. Reckless, G. Davies, K. Tunceli, X. H. Hu and P. Brudi.Projected cost-effectiveness of ezetimibe/simvastatin compared with doubling the statin dose in the United Kingdom: findings from the INFORCE study. Value Health 2010: 726-34

T. Bader.The myth of statin-induced hepatotoxicity. Am J Gastroenterol 2010: 978-80

A. Tomillero and M. A. Moral.Gateways to clinical trials. Methods Find Exp Clin Pharmacol 2010: 133-47

C. M. Ferrario.ARBITER 6-HALTS. Does it have the power to settle all matters?. Ther Adv Cardiovasc Dis 2010: 77-81

S. Conard, H. Bays, L. A. Leiter, S. Bird, J. Lin, M. E. Hanson, A. Shah and A. M. Tershakovec.Ezetimibe added to atorvastatin compared with doubling the atorvastatin dose in patients at high risk for coronary heart disease with diabetes mellitus, metabolic syndrome or neither. Diabetes Obes Metab 2010: 210-8

R. B. Goldberg, J. R. Guyton, T. Mazzone, R. S. Weinstock, A. B. Polis, D. Tipping, J. E. Tomassini and A. M. Tershakovec.Relationships between metabolic syndrome and other baseline factors and the efficacy of ezetimibe/simvastatin and atorvastatin in patients with type 2 diabetes and hypercholesterolemia. Diabetes Care 2010: 1021-4

P. H. Jones, K. Cusi, M. H. Davidson, M. T. Kelly, C. M. Setze, K. Thakker, D. J. Sleep and J. C. Stolzenbach.Efficacy and safety of fenofibric acid co-administered with low- or moderate-dose statin in patients with mixed dyslipidemia and type 2 diabetes mellitus: results of a pooled subgroup analysis from three randomized, controlled, double-blind trials. Am J Cardiovasc Drugs 2010: 73-84

X. Q. Zhao, R. A. Krasuski, J. Baer, E. J. Whitney, B. Neradilek, A. Chait, S. Marcovina, J. J. Albers and B. G. Brown.Effects of combination lipid therapy on coronary stenosis progression and clinical cardiovascular events in coronary disease patients with metabolic syndrome: a combined analysis of the Familial Atherosclerosis Treatment Study (FATS), the HDL-Atherosclerosis Treatment Study (HATS), and the Armed Forces Regression Study (AFREGS). Am J Cardiol 2009: 1457-64

A. B. Polis, N. Abate, A. L. Catapano, C. M. Ballantyne, M. H. Davidson, S. S. Smugar and A. M. Tershakovec.Low-density lipoprotein cholesterol reduction and goal achievement with ezetimibe/simvastatin versus atorvastatin or rosuvastatin in patients with diabetes, metabolic syndrome, or neither disease, stratified by National Cholesterol Education Program risk category. Metab Syndr Relat Disord 2009: 601-10

J. J. Kastelein and M. L. Bots.Statin therapy with ezetimibe or niacin in high-risk patients. N Engl J Med 2009: 2180-3

J. Farmer.The Vytorin on Carotid-Media Thickness and Overall Arterial Rigidity (VYCTOR) study. Expert Rev Cardiovasc Ther 2009: 1057-60

G. Steiner.How can we improve the management of vascular risk in type 2 diabetes: insights from FIELD. Cardiovasc Drugs Ther 2009: 403-8

D. Miller.Fear of statins?. CMAJ 2009: 399

R. M. Califf, R. A. Harrington and M. A. Blazing.Premature release of data from clinical trials of ezetimibe. N Engl J Med 2009: 712-7

.Statins reduce stroke risk by one-fifth. Cardiovasc J Afr 2009: 208-9

G. S. Goumas.LDL-Cholesterol is the King. Angiology 2009: 387-8

P. H. Jones, M. H. Davidson, A. C. Goldberg, C. J. Pepine, M. T. Kelly, S. M. Buttler, C. M. Setze, A. Lele, D. J. Sleep and J. C. Stolzenbach.Efficacy and safety of fenofibric acid in combination with a statin in patients with mixed dyslipidemia: Pooled analysis of three phase 3, 12-week randomized, controlled studies. J Clin Lipidol 2009: 125-37

J. A. Farmer.Simvastatin with or without ezetimibe in familial hypercholesterolemia (the ENHANCE trial). Curr Atheroscler Rep 2009: 81-2

H. E. Bays, P. H. Jones, S. M. Mohiuddin, M. T. Kelly, H. Sun, C. M. Setze, S. M. Buttler, D. J. Sleep and J. C. Stolzenbach.Long-term safety and efficacy of fenofibric acid in combination with statin therapy for the treatment of patients with mixed dyslipidemia. J Clin Lipidol 2008: 426-35

A. N. Vo and M. L. Kashyap.Fixed-dose combination of extended-release niacin plus simvastatin for lipid disorders. Expert Rev Cardiovasc Ther 2008: 1303-10

N. Donner-Banzhoff and A. Sonnichsen.Statins and primary prevention of cardiovascular events. BMJ 2008: a2576

R. Dobson.Trial stopped early after rosuvastatin found to cut the risk of heart attack and stroke by 44% in healthy people. BMJ 2008: a2523

R. L. Wilensky.Vulnerable plaque: scope of the problem. J Interv Cardiol 2008: 443-51

H. N. Ginsberg and R. Ramakrishnan.Kinetic studies of the metabolism of rapidly exchangeable apolipoproteins may leave investigators and readers with exchangeable results. Arterioscler Thromb Vasc Biol 2008: 1685-6

T. R. Fleming.Identifying and addressing safety signals in clinical trials. N Engl J Med 2008: 1400-2

R. Peto, J. Emberson, M. Landray, C. Baigent, R. Collins, R. Clare and R. Califf.Analyses of cancer data from three ezetimibe trials. N Engl J Med 2008: 1357-66

J. H. O'Keefe, K. A. Bybee and C. J. Lavie.Intensive lipid intervention in the post-ENHANCE era. Mayo Clin Proc 2008: 867-9

P. Toutouzas and D. Richter.Carotid intima-media thickness (cIMT): a useful clinic tool or research luxury? Another view of the ENHANCE trial. Angiology 2008: 77S-9S

.ENHANCE results: a surrogate trial that impacts beyond size and scope. Cardiovasc J Afr 2008: 166-8

V. L. Serebruany.Controlled Rosuvastatin Multinational Trial In Heart Failure (the positive negative trial). Am J Cardiol 2008: 1808-9

N. Abate, A. L. Catapano, C. M. Ballantyne, M. H. Davidson, A. Polis, S. S. Smugar and A. M. Tershakovec.Effect of ezetimibe/simvastatin versus atorvastatin or rosuvastatin on modifying lipid profiles in patients with diabetes, metabolic syndrome, or neither: Results of two subgroup analyses. J Clin Lipidol 2008: 91-105

J. G. Karam, L. Loney-Hutchinson and S. I. McFarlane.High-dose atorvastatin after stroke or transient ischemic attack: The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators. J Cardiometab Syndr 2008: 68-9

.Extended ASCOT - lipid lowering (ASCOT-LLA) study shows positive results of atorvastatin. Cardiovasc J Afr 2008: 49-51

R. S. Weinstock, R. B. Goldberg, J. R. Guyton, T. Mazzone, A. Polis, J. E. Tomassini, J. Lin, A. Shah and A. M. Tershakovec.Effect of ezetimibe/simvastatin vs atorvastatin on lowering levels of LDL-C and non-HDL-C, ApoB, and hs-CRP in patients with type 2 diabetes. J Clin Lipidol 2008: 25-35

G. Assmann, F. Kannenberg, D. R. Ramey, T. A. Musliner, S. W. Gutkin and E. P. Veltri.Effects of ezetimibe, simvastatin, atorvastatin, and ezetimibe-statin therapies on non-cholesterol sterols in patients with primary hypercholesterolemia. Curr Med Res Opin 2008: 249-59

Tomillero, A. and Moral, M. A..Summary. Methods Find. Exp. Clin. Pharmacol. 2010 :331-388

Davidson, M. H..Should niacin be the preferred drug to add to a statin?. Curr. Cardiol. Rep. 2010 :447-449

Reiner, Z..Combination therapy with prescription omega-3-acid ethyl esters and statin improves non-HDL-C more effectively than statin alone. Clinical Lipidology 2010 :325-328

Kastelein, J. J. P. and Bots, M. L..Statin therapy with ezetimibe or niacin in high-risk patients. New Engl. J. Med. 2009 :2180-2183

Yasu, T..JELIS study. Jpn. J. Clin. Pharmacol. Ther. 2008 :167-168

Wiklund, O., Bondjers, G., Wright, I., and Camejo, G..Insoluble complex formation between LDL and arterial proteoglycans in relation to serum lipid levels and effects of lipid lowering drugs. Atherosclerosis 96 :57-67

Pearson, T., Ballantyne, C., Sisk, C., Shah, A., Veltri, E., and Maccubbin, D..Comparison of effects of ezetimibe/simvastatin versus simvastatin versus atorvastatin in reducing C-reactive protein and low-density lipoprotein cholesterol levels. Am J Cardiol 2007 :1706-1713

Tanaka, K., Ishikawa, Y., Yokoyama, M., Origasa, H., Matsuzaki, M., Saito, Y., Matsuzawa, Y., Sasaki, J., Oikawa, S., Hishida, H., Itakura, H., Kita, T., Kitabatake, A., Nakaya, N., Sakata, T., Shimada, K., and Shirato, K..Reduction in the recurrence of stroke by eicosapentaenoic acid for hypercholesterolemic patients: subanalysis of the JELIS trial. Stroke 2008 :2052-8

Taylor, A. J., Zhu, D., Sullenberger, L. E., Lee, H. J., Lee, J. K., and Grace, K. A..Relationship between glycemic status and progression of carotid intima-media thickness during treatment with combined statin and extended-release niacin in ARBITER 2. Vasc Health Risk Manag 2007 :159-64

Abate, N., Catapano, A. L., Ballantyne, C. M., Davidson, M. H., Polis, A., Smugar, S. S., and Tershakovec, A. M..Effect of ezetimibe/simvastatin versus atorvastatin or rosuvastatin on modifying lipid profiles in patients with diabetes, metabolic syndrome, or neither: Results of two subgroup analyses. J Clin Lipidol 2008 :91-105

Not Full Report

J. Farmer.The Vytorin on Carotid-Media Thickness and Overall Arterial Rigidity (VYCTOR) study. Expert Rev Cardiovasc Ther 2009: 1057-60

Toyama, K., Sasaki, O., Nishioka, T., and Ito, H..Beneficial effect of eicosapentaenoic acid on endothelial function in old myocardial infarction patients under adequate statin therapy. J. Am. Coll. Cardiol. 2012 :E1773

Dobs, et al.[Randomised double-blind dosetitration (to target low-density lipoprotein cholesterol) Phase 3 evaluation ... provisional acceptance] [abstract]. J Am Coll Cardiol 2003 :227A

Not in English

E. Namal, N. Sener, T. Ulas, Z. Akcali, E. Oztekin and F. Borlu.[Effects of different statins, ezetimibe/simvastatin combination on hsCRP levels in unstable angina pectoris and non-ST elevation myocardial infarction patients: a randomized trial]. Anadolu Kardiyol Derg 2011: 703-10

Karbasi-Afshar, R., Shahmari, A., Shafighi, N., and Saburi, A..Effects of simvastatin with or without fenofibrate on echocardiographic findings of patients with coronary artery disease and dyslipidemia: A brief report. Tehran Uni. Med. J. 2012 :378-382

Safarova, M., Trukhacheva, E., Ezhov, M., Afanasieva, O., Tripoten, M., and Pokrovsky, S..Pleiotropic effects of niacin therapy in addition to atorvastatin in coronary heart disease patients with elevated lipoprotein(A) levels. Atheroscler. Suppl. 2011 :69

Yasu, T..JELIS study. Jpn. J. Clin. Pharmacol. Ther. 2008 :167-168

Yamagishi, T..[Efficacy and safety of ezetimibe added on to rosuvastatin (2.5 mg) compared with uptitration of rosuvastatin (5 mg) in hyperlipidemic patients] LA: Jpn. Japanese Pharmacology and Therapeutics 2010 :305-11

Dobs, et al.[Randomised double-blind dosetitration (to target low-density lipoprotein cholesterol) Phase 3 evaluation ... provisional acceptance] [abstract]. J Am Coll Cardiol 2003 :227A

Children Study

A. van der Graaf, C. Cuffie-Jackson, M. N. Vissers, M. D. Trip, C. Gagne, G. Shi, E. Veltri, H. J. Avis and J. J. Kastelein.Efficacy and safety of coadministration of ezetimibe and simvastatin in adolescents with heterozygous familial hypercholesterolemia. J Am Coll Cardiol 2008: 1421-9

Healthy Subjects

A. Zinellu, S. Sotgia, G. Loriga, L. Deiana, A. E. Satta and C. Carru.Oxidative stress improvement is associated with increased levels of taurine in CKD patients undergoing lipid-lowering therapy. Amino Acids 2012: 1499-507

J. G. Robinson, C. M. Ballantyne, W. Hsueh, J. Rosen, J. Lin, A. Shah, R. S. Lowe, M. E. Hanson and A. M. Tershakovec.Achievement of specified low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol apolipoprotein B, and high-sensitivity C-reactive protein levels with ezetimibe/simvastatin or atorvastatin in metabolic syndrome patients with and without atherosclerotic vascular disease (from the VYMET study). J Clin Lipidol 2011: 474-82

P. Y. Liu, Y. W. Liu, L. J. Lin, J. H. Chen and J. K. Liao.Evidence for statin pleiotropy in humans: differential effects of statins and ezetimibe on rho-associated coiled-coil containing protein kinase activity, endothelial function, and inflammation. Circulation 2009: 131-8

Kosoglou, T., Meyer, I., Veltri, E. P., Statkevich, P., Yang, B., Zhu, Y., Mellars, L., Maxwell, S. E., Patrick, J. E., Cutler, D. L., Batra, V. K., and Affrime, M. B..Pharmacodynamic interaction between the new selective cholesterol absorption inhibitor ezetimibe and simvastatin. Br J Clin Pharmacol 2002 :309-19

Not RCT or Extension

G. Reyes-Soffer, C. I. Ngai, L. Lovato, W. Karmally, R. Ramakrishnan, S. Holleran and H. N. Ginsberg.Effect of Combination Therapy With Fenofibrate and Simvastatin on Postprandial Lipemia in the ACCORD Lipid Trial. Diabetes Care 2013: 422-8

A. Tenenbaum, D. Medvedofsky, E. Z. Fisman, L. Bubyr, S. Matetzky, D. Tanne, R. Klempfner, J. Shemesh and I. Goldenberg.Cardiovascular events in patients received combined fibrate/statin treatment versus statin monotherapy: Acute Coronary Syndrome Israeli Surveys data. PLoS One 2012: e35298

Y. Sawayama, S. Maeda, H. Ohnishi, S. Hayashi and J. Hayashi.Efficacy and safety of ezetimibe for Japanese patients with dyslipidaemia: The ESSENTIAL Study. Clin Drug Investig 2010: 157-66

T. Abel, J. Feher, E. Dinya, M. G. Eldin and A. Kovacs.Safety and efficacy of combined ezetimibe/simvastatin treatment and simvastatin monotherapy in patients with non-alcoholic fatty liver disease. Med Sci Monit 2009: MS6-11

G. Derosa, A. D'Angelo, I. G. Franzetti, P. D. Ragonesi, G. Gadaleta, F. Scalise, L. Ciccarelli, M. N. Piccinni and A. F. Cicero.Efficacy and safety of ezetimibe/simvastatin association on non-diabetic and diabetic patients with polygenic hypercholesterolemia or combined hyperlipidemia and previously intolerant to standard statin treatment. J Clin Pharm Ther 2009: 267-76

D. Poldermans, M. Dunkelgrun, O. Schouten and U. Hostalek.Prolonged-release nicotinic acid in patients with atherosclerotic disease in the Netherlands. Eur Surg Res 2008: 313-8

B. Liska, A. A. Khattab, L. Herrmann, M. Abdel-Wahab, R. Westphal, R. Tolg, V. Geist and G. Richardt.Simvastatin and ezetimibe in addition to nonpharmacological risk factor modification for achieving new low-density lipoprotein cholesterol targets. Herz 2008: 362-7

J. Mayne, T. Dewpura, A. Raymond, M. Cousins, A. Chaplin, K. A. Lahey, S. A. Lahaye, M. Mbikay, T. C. Ooi and M. Chretien.Plasma PCSK9 levels are significantly modified by statins and fibrates in humans. Lipids Health Dis 2008: 22

Drug Is Not Approved

C. Ballantyne, G. Gleim, N. Liu, C. M. Sisk, A. O. Johnson-Levonas and Y. Mitchel.Effects of coadministered extended-release niacin/laropiprant and simvastatin on lipoprotein subclasses in patients with dyslipidemia. J Clin Lipidol 2012: 235-43

Not Relevant to Key Question

E. Bahlmann, E. Gerdts, D. Cramariuc, C. Gohlke-Baerwolf, C. A. Nienaber, K. Wachtell, R. Seifert, J. B. Chambers, K. H. Kuck and S. Ray.Prognostic Value of Energy Loss Index in Asymptomatic Aortic Stenosis. Circulation 2013:

J. G. Jimenez, J. B. Rosen, V. Pirags, R. Massaad, M. E. Hanson, P. Brudi and J. Triscari.The efficacy and safety of ezetimibe/simvastatin combination compared with intensified lipid-lowering treatment strategies in diabetic subjects with and without metabolic syndrome. Diabetes Obes Metab 2012:

K. Kinouchi, A. Ichihara, K. Bokuda, S. Morimoto and H. Itoh.Effects of Adding Ezetimibe to Fluvastatin on Kidney Function in Patients with Hypercholesterolemia: a Randomized Control Trial. J Atheroscler Thromb 2012:

A. C. Philpott, J. Hubacek, Y. C. Sun, D. Hillard and T. J. Anderson.Niacin improves lipid profile but not endothelial function in patients with coronary artery disease on high dose statin therapy. Atherosclerosis 2013: 453-8

H. K. Berthold, K. Berneis, C. S. Mantzoros, W. Krone and I. Gouni-Berthold.Effects of simvastatin and ezetimibe on interleukin-6 and high-sensitivity C-reactive protein. Scand Cardiovasc J 2013: 20-7

L. Buldak, A. Dulawa-Buldak, K. Labuzek and B. Okopien.Effects of 90-day hypolipidemic treatment on insulin resistance, adipokines and proinflammatory cytokines in patients with mixed hyperlipidemia and impaired fasting glucose. Int J Clin Pharmacol Ther 2012: 805-13

C. M. Ballantyne, H. E. Bays, J. J. Kastelein, E. Stein, J. L. Isaacsohn, R. A. Braeckman and P. N. Soni.Efficacy and safety of eicosapentaenoic acid ethyl ester (AMR101) therapy in statin-treated patients with persistent high triglycerides (from the ANCHOR study). Am J Cardiol 2012: 984-92

G. N. Kouvelos, E. M. Arnaoutoglou, M. I. Matsagkas, C. Kostara, C. Gartzonika, E. T. Bairaktari and H. J. Milionis.Effects of rosuvastatin with or without ezetimibe on clinical outcomes in patients undergoing elective vascular surgery: results of a pilot study. J Cardiovasc Pharmacol Ther 2013: 5-12

T. Arimura, S. Miura, A. Ike, M. Sugihara, A. Iwata, H. Nishikawa, A. Kawamura and K. Saku.Comparison of the efficacy and safety of statin and statin/ezetimibe therapy after coronary stent implantation in patients with stable angina. J Cardiol 2012: 111-8

J. R. Guyton, S. Fazio, A. J. Adewale, E. Jensen, J. E. Tomassini, A. Shah and A. M. Tershakovec.Effect of extended-release niacin on new-onset diabetes among hyperlipidemic patients treated with ezetimibe/simvastatin in a randomized controlled trial. Diabetes Care 2012: 857-60

P. P. Toth, K. M. Thakker, P. Jiang and R. J. Padley.Niacin extended-release/simvastatin combination therapy produces larger favorable changes in high-density lipoprotein particles than atorvastatin monotherapy. Vasc Health Risk Manag 2012: 39-44

J. Sasaki, T. Miwa and M. Odawara.Administration of highly purified eicosapentaenoic acid to statin-treated diabetic patients further improves vascular function. Endocr J 2012: 297-304

P. K. Hing Ling, F. Civeira, A. G. Dan, M. E. Hanson, R. Massaad, B. De Tilleghem Cle, C. Milardo and J. Triscari.Ezetimibe/simvastatin 10/40 mg versus atorvastatin 40 mg in high cardiovascular risk patients with primary hypercholesterolemia: a randomized, double-blind, active-controlled, multicenter study. Lipids Health Dis 2012: 18

J. Sasaki, M. Yokoyama, M. Matsuzaki, Y. Saito, H. Origasa, Y. Ishikawa, S. Oikawa, H. Itakura, H. Hishida, T. Kita, A. Kitabatake, N. Nakaya, T. Sakata, K. Shimada, K. Shirato and Y. Matsuzawa.Relationship between coronary artery disease and non-HDL-C, and effect of highly purified EPA on the risk of coronary artery disease in hypercholesterolemic patients treated with statins: sub-analysis of the Japan EPA Lipid Intervention Study (JELIS). J Atheroscler Thromb 2012: 194-204

W. Elmallah and R. A. Krasuski.Therapy and clinical trials. Curr Opin Lipidol 2011: 512-3

M. Farnier, Q. Dong, A. Shah, A. O. Johnson-Levonas and P. Brudi.Low incidence of paradoxical reductions in HDL-C levels in dyslipidemic patients treated with fenofibrate alone or in combination with ezetimibe or ezetimibe/simvastatin. Lipids Health Dis 2011: 212

W. E. Boden, J. L. Probstfield, T. Anderson, B. R. Chaitman, P. Desvignes-Nickens, K. Koprowicz, R. McBride, K. Teo and W. Weintraub.Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. N Engl J Med 2011: 2255-67

C. M. Ballantyne, M. H. Davidson, C. M. Setze and M. T. Kelly.Effects of combination therapy with rosuvastatin and fenofibric acid in patients with mixed dyslipidemia and high-sensitivity C-reactive protein (>/= 2 mg/L). cmb@bcm.tmc.edu. J Clin Lipidol 2011: 401-7

A. Brautbar, D. Covarrubias, J. Belmont, F. Lara-Garduno, S. S. Virani, P. H. Jones, S. M. Leal and C. M. Ballantyne.Variants in the APOA5 gene region and the response to combination therapy with statins and fenofibric acid in a randomized clinical trial of individuals with mixed dyslipidemia. Atherosclerosis 2011: 737-42

R. Tsunoda, T. Sakamoto, S. Kojima, Y. Ogata, A. Kitagwa and H. Ogawa.Recurrence of angina pectoris after percutaneous coronary intervention is reduced by statins in Japanese patients. J Cardiol 2011: 208-15

J. P. Schuchardt, J. Neubronner, G. Kressel, M. Merkel, C. von Schacky and A. Hahn.Moderate doses of EPA and DHA from re-esterified triacylglycerols but not from ethyl-esters lower fasting serum triacylglycerols in statin-treated dyslipidemic subjects: Results from a six month randomized controlled trial. Prostaglandins Leukot Essent Fatty Acids 2011: 381-6

H. Takagi, M. Matsui and T. Umemoto.High-density lipoprotein-dependent effects of statins on the risk of coronary heart disease deaths and events. Int J Cardiol 2011: 377-9

S. C. Ramos, F. A. Fonseca, S. H. Kasmas, F. T. Moreira, T. Helfenstein, N. C. Borges, R. A. Moreno, V. M. Rezende, F. C. Silva and M. C. Izar.The role of soluble fiber intake in patients under highly effective lipid-lowering therapy. Nutr J 2011: 80

P. S. Sever, N. R. Poulter, C. L. Chang, A. Hingorani, S. A. Thom, A. D. Hughes, P. Welsh and N. Sattar.Evaluation of C-reactive protein prior to and on-treatment as a predictor of benefit from atorvastatin: observations from the Anglo-Scandinavian Cardiac Outcomes Trial. Eur Heart J 2012: 486-94

I. Idris, H. Tate, A. Ahmad and T. McCormack.Concordance between plasma apolipoprotein B levels and cholesterol indices among patients receiving statins and nonstatin treatment: Post-hoc analyses from the U.K. InPractice study. J Clin Lipidol 2011: 316-23

H. E. Bays, C. M. Ballantyne, J. J. Kastelein, J. L. Isaacsohn, R. A. Braeckman and P. N. Soni.Eicosapentaenoic acid ethyl ester (AMR101) therapy in patients with very high triglyceride levels (from the Multi-center, plAcebo-controlled, Randomized, double-blINd, 12-week study with an open-label Extension [MARINE] trial). Am J Cardiol 2011: 682-90

R. Krysiak, W. Zmuda and B. Okopien.The effect of ezetimibe, administered alone or in combination with simvastatin, on lymphocyte cytokine release in patients with elevated cholesterol levels. J Intern Med 2012: 32-42

M. Farnier, W. Taggart, Q. Dong, J. Lin, A. Shah and P. Brudi.Influence of simvastatin, fenofibrate and/or ezetimibe on correlation of low-density lipoprotein and nonhigh-density lipoprotein cholesterol with apolipoprotein B in mixed dyslipidemic patients. J Clin Lipidol 2011: 179-87

A. M. West, J. D. Anderson, C. H. Meyer, F. H. Epstein, H. Wang, K. D. Hagspiel, S. S. Berr, N. L. Harthun, J. M. DiMaria, J. R. Hunter, J. M. Christopher, J. D. Chew, G. B. Winberry and C. M. Kramer.The effect of ezetimibe on peripheral arterial atherosclerosis depends upon statin use at baseline. Atherosclerosis 2011: 156-62

L. Dong, W. S. Kerwin, H. Chen, B. Chu, H. R. Underhill, M. B. Neradilek, T. S. Hatsukami, C. Yuan and X. Q. Zhao.Carotid artery atherosclerosis: effect of intensive lipid therapy on the vasa vasorum--evaluation by using dynamic contrast-enhanced MR imaging. Radiology 2011: 224-31

.The role of niacin in raising high-density lipoprotein cholesterol to reduce cardiovascular events in patients with atherosclerotic cardiovascular disease and optimally treated low-density lipoprotein cholesterol: baseline characteristics of study participants. The Atherothrombosis Intervention in Metabolic syndrome with low HDL/high triglycerides: impact on Global Health outcomes (AIM-HIGH) trial. Am Heart J 2011: 538-43

.The role of niacin in raising high-density lipoprotein cholesterol to reduce cardiovascular events in patients with atherosclerotic cardiovascular disease and optimally treated low-density lipoprotein cholesterol Rationale and study design. The Atherothrombosis Intervention in Metabolic syndrome with low HDL/high triglycerides: Impact on Global Health outcomes (AIM-HIGH). Am Heart J 2011: 471-477 e2

R. Krysiak and B. Okopien.The effect of ezetimibe and simvastatin on monocyte cytokine release in patients with isolated hypercholesterolemia. J Cardiovasc Pharmacol 2011: 505-12

M. Dobiasova, J. Frohlich, M. Sedova, M. C. Cheung and B. G. Brown.Cholesterol esterification and atherogenic index of plasma correlate with lipoprotein size and findings on coronary angiography. J Lipid Res 2011: 566-71

R. S. Rosenson, D. M. Carlson, M. T. Kelly, C. M. Setze, B. Hirshberg, J. C. Stolzenbach and L. A. Williams.Achievement of lipid targets with the combination of rosuvastatin and fenofibric Acid in patients with type 2 diabetes mellitus. Cardiovasc Drugs Ther 2011: 47-57

S. H. Kim, K. Park, S. J. Hong, Y. S. Cho, J. D. Sung, G. W. Moon, M. H. Yoon, M. Y. Lee, M. S. Hyon, D. W. Kim and H. S. Kim.Efficacy and tolerability of a generic and a branded formulation of atorvastatin 20 mg/d in hypercholesterolemic Korean adults at high risk for cardiovascular disease: a multicenter, prospective, randomized, double-blind, double-dummy clinical trial. Clin Ther 2010: 1896-905

M. Viigimaa, H. Vaverkova, M. Farnier, M. Averna, L. Missault, M. E. Hanson, Q. Dong, A. Shah and P. Brudi.Ezetimibe/simvastatin 10/20 mg versus rosuvastatin 10 mg in high-risk hypercholesterolemic patients stratified by prior statin treatment potency. Lipids Health Dis 2010: 127

C. J. Pepine, T. A. Jacobson, D. M. Carlson, M. T. Kelly, C. M. Setze, A. Gold, J. C. Stolzenbach and L. A. Williams.Combination rosuvastatin plus fenofibric acid in a cohort of patients 65 years or older with mixed dyslipidemia: subanalysis of two randomized, controlled studies. Clin Cardiol 2010: 609-19

L. A. Leiter, H. Bays, S. Conard, J. Lin, M. E. Hanson, A. Shah and A. M. Tershakovec.Attainment of Canadian and European guidelines' lipid targets with atorvastatin plus ezetimibe vs. doubling the dose of atorvastatin. Int J Clin Pract 2010: 1765-72

H. Vaverkova, M. Farnier, M. Averna, L. Missault, M. Viigimaa, Q. Dong, A. Shah, A. O. Johnson-Levonas and P. Brudi.Lipid-altering efficacy of ezetimibe/simvastatin 10/20 mg compared to rosuvastatin 10 mg in high-risk patients with and without type 2 diabetes mellitus inadequately controlled despite prior statin monotherapy. Cardiovasc Ther 2012: 61-74

J. Reckless, G. Davies, K. Tunceli, X. H. Hu and P. Brudi.Projected cost-effectiveness of ezetimibe/simvastatin compared with doubling the statin dose in the United Kingdom: findings from the INFORCE study. Value Health 2010: 726-34

T. McCormack, P. Harvey, R. Gaunt, V. Allgar, R. Chipperfield and P. Robinson.Incremental cholesterol reduction with ezetimibe/simvastatin, atorvastatin and rosuvastatin in UK General Practice (IN-PRACTICE): randomised controlled trial of achievement of Joint British Societies (JBS-2) cholesterol targets. Int J Clin Pract 2010: 1052-61

K. C. Maki, M. R. Dicklin, M. H. Davidson, R. T. Doyle and C. M. Ballantyne.Baseline lipoprotein lipids and low-density lipoprotein cholesterol response to prescription omega-3 acid ethyl ester added to Simvastatin therapy. Am J Cardiol 2010: 1409-12

T. C. Villines, E. J. Stanek, P. J. Devine, M. Turco, M. Miller, N. J. Weissman, L. Griffen and A. J. Taylor.The ARBITER 6-HALTS Trial (Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6-HDL and LDL Treatment Strategies in Atherosclerosis): final results and the impact of medication adherence, dose, and treatment duration. J Am Coll Cardiol 2010: 2721-6

C. M. Ferrario.ARBITER 6-HALTS. Does it have the power to settle all matters?. Ther Adv Cardiovasc Dis 2010: 77-81

A. L. Kater, M. C. Batista and S. R. Ferreira.Improved endothelial function with simvastatin but unchanged insulin sensitivity with simvastatin or ezetimibe. Metabolism 2010: 921-6

H. E. Bays, K. C. Maki, J. McKenney, R. Snipes, A. Meadowcroft, R. Schroyer, R. T. Doyle and E. Stein.Long-term up to 24-month efficacy and safety of concomitant prescription omega-3-acid ethyl esters and simvastatin in hypertriglyceridemic patients. Curr Med Res Opin 2010: 907-15

Y. Sawayama, S. Maeda, H. Ohnishi, S. Hayashi and J. Hayashi.Efficacy and safety of ezetimibe for Japanese patients with dyslipidaemia: The ESSENTIAL Study. Clin Drug Investig 2010: 157-66

S. Fazio, J. R. Guyton, A. B. Polis, A. J. Adewale, J. E. Tomassini, N. W. Ryan and A. M. Tershakovec.Long-term safety and efficacy of triple combination ezetimibe/simvastatin plus extended-release niacin in patients with hyperlipidemia. Am J Cardiol 2010: 487-94

H. Origasa, M. Yokoyama, M. Matsuzaki, Y. Saito and Y. Matsuzawa.Clinical importance of adherence to treatment with eicosapentaenoic acid by patients with hypercholesterolemia. Circ J 2010: 510-7

H. E. Bays, J. McKenney, K. C. Maki, R. T. Doyle, R. N. Carter and E. Stein.Effects of prescription omega-3-acid ethyl esters on non--high-density lipoprotein cholesterol when coadministered with escalating doses of atorvastatin. Mayo Clin Proc 2010: 122-8

M. H. Davidson, M. W. Rooney, J. Drucker, H. Eugene Griffin, S. Oosman and M. Beckert.Efficacy and tolerability of atorvastatin/fenofibrate fixed-dose combination tablet compared with atorvastatin and fenofibrate monotherapies in patients with dyslipidemia: a 12-week, multicenter, double-blind, randomized, parallel-group study. Clin Ther 2009: 2824-38

S. S. Kumar, K. A. Lahey, A. Day and S. A. LaHaye.Comparison of the efficacy of administering a combination of ezetimibe plus fenofibrate versus atorvastatin monotherapy in the treatment of dyslipidemia. Lipids Health Dis 2009: 56

M. S. Kipnes, E. M. Roth, J. M. Rhyne, C. M. Setze, A. Lele, M. T. Kelly, D. J. Sleep and J. C. Stolzenbach.Year two assessment of fenofibric acid and moderate-dose statin combination: a phase 3, open-label, extension study. Clin Drug Investig 2010: 51-61

S. G. Lakoski, F. Xu, G. L. Vega, S. M. Grundy, M. Chandalia, C. Lam, R. S. Lowe, M. E. Stepanavage, T. A. Musliner, J. C. Cohen and H. H. Hobbs.Indices of cholesterol metabolism and relative responsiveness to ezetimibe and simvastatin. J Clin Endocrinol Metab 2010: 800-9

X. Q. Zhao, R. A. Krasuski, J. Baer, E. J. Whitney, B. Neradilek, A. Chait, S. Marcovina, J. J. Albers and B. G. Brown.Effects of combination lipid therapy on coronary stenosis progression and clinical cardiovascular events in coronary disease patients with metabolic syndrome: a combined analysis of the Familial Atherosclerosis Treatment Study (FATS), the HDL-Atherosclerosis Treatment Study (HATS), and the Armed Forces Regression Study (AFREGS). Am J Cardiol 2009: 1457-64

A. B. Polis, N. Abate, A. L. Catapano, C. M. Ballantyne, M. H. Davidson, S. S. Smugar and A. M. Tershakovec.Low-density lipoprotein cholesterol reduction and goal achievement with ezetimibe/simvastatin versus atorvastatin or rosuvastatin in patients with diabetes, metabolic syndrome, or neither disease, stratified by National Cholesterol Education Program risk category. Metab Syndr Relat Disord 2009: 601-10

L. Jakulj, M. N. Vissers, A. K. Groen, B. A. Hutten, D. Lutjohann, E. P. Veltri and J. J. Kastelein.Baseline cholesterol absorption and the response to ezetimibe/simvastatin therapy: a post-hoc analysis of the ENHANCE trial. J Lipid Res 2010: 755-62

M. Florentin, M. S. Kostapanos, E. S. Nakou, M. Elisaf and E. N. Liberopoulos.Efficacy and safety of ezetimibe plus orlistat or rimonabant in statin-intolerant nondiabetic overweight/obese patients with dyslipidemia. J Cardiovasc Pharmacol Ther 2009: 274-82

Z. C. Sang, F. Wang, Q. Zhou, Y. H. Li, Y. G. Li, H. P. Wang and S. Y. Chen.Combined use of extended-release niacin and atorvastatin: safety and effects on lipid modification. Chin Med J (Engl) 2009: 1615-20

T. Nakamura, E. Sato, N. Fujiwara, Y. Kawagoe, Y. Ueda, T. Suzuki, S. Ueda, K. Fukami, S. Okuda and S. Yamagishi.Co-administration of ezetimibe enhances proteinuria-lowering effects of pitavastatin in chronic kidney disease patients partly via a cholesterol-independent manner. Pharmacol Res 2010: 58-61

G. Derosa, A. D'Angelo, I. G. Franzetti, P. D. Ragonesi, G. Gadaleta, F. Scalise, L. Ciccarelli, M. N. Piccinni and A. F. Cicero.Efficacy and safety of ezetimibe/simvastatin association on non-diabetic and diabetic patients with polygenic hypercholesterolemia or combined hyperlipidemia and previously intolerant to standard statin treatment. J Clin Pharm Ther 2009: 267-76

M. Settergren, F. Bohm, L. Ryden, J. Pernow and M. Kalani.Lipid lowering versus pleiotropic effects of statins on skin microvascular function in patients with dysglycaemia and coronary artery disease. J Intern Med 2009: 492-8

G. Derosa, P. Maffioli, S. A. Salvadeo, I. Ferrari, A. Gravina, R. Mereu, I. Palumbo, A. D'Angelo and A. F. Cicero.Fenofibrate, simvastatin and their combination in the management of dyslipidaemia in type 2 diabetic patients. Curr Med Res Opin 2009: 1973-83

S. Oikawa, M. Yokoyama, H. Origasa, M. Matsuzaki, Y. Matsuzawa, Y. Saito, Y. Ishikawa, J. Sasaki, H. Hishida, H. Itakura, T. Kita, A. Kitabatake, N. Nakaya, T. Sakata, K. Shimada and K. Shirato.Suppressive effect of EPA on the incidence of coronary events in hypercholesterolemia with impaired glucose metabolism: Sub-analysis of the Japan EPA Lipid Intervention Study (JELIS). Atherosclerosis 2009: 535-9

M. Matsuzaki, M. Yokoyama, Y. Saito, H. Origasa, Y. Ishikawa, S. Oikawa, J. Sasaki, H. Hishida, H. Itakura, T. Kita, A. Kitabatake, N. Nakaya, T. Sakata, K. Shimada, K. Shirato and Y. Matsuzawa.Incremental effects of eicosapentaenoic acid on cardiovascular events in statin-treated patients with coronary artery disease. Circ J 2009: 1283-90

K. Winkler, T. Schewe, G. Putz, N. Odunc, G. Schafer, E. Siegel, U. Geisen, C. Abletshauser and M. M. Hoffmann.Fluvastatin/fenofibrate vs. simvastatin/ezetimibe in patients with metabolic syndrome: different effects on LDL-profiles. Eur J Clin Invest 2009: 463-70

T. Sudhop, M. Reber, D. Tribble, A. Sapre, W. Taggart, P. Gibbons, T. Musliner, K. von Bergmann and D. Lutjohann.Changes in cholesterol absorption and cholesterol synthesis caused by ezetimibe and/or simvastatin in men. J Lipid Res 2009: 2117-23

M. J. Zema.Add-on therapy for hypercholesterolemia: a pilot comparison of two gastrointestinally-acting agents in statin-treated patients. J Clin Lipidol 2009: 119-24

A. J. Tremblay, B. Lamarche, J. C. Hogue and P. Couture.Effects of ezetimibe and simvastatin on apolipoprotein B metabolism in males with mixed hyperlipidemia. J Lipid Res 2009: 1463-71

K. C. Maki, B. C. Lubin, M. S. Reeves, M. R. Dicklin and W. S. Harris.Prescription omega-3 acid ethyl esters plus simvastatin 20 and 80 mg: effects in mixed dyslipidemia. J Clin Lipidol 2009: 33-8

S. Nomura, N. Inami, A. Shouzu, S. Omoto, Y. Kimura, N. Takahashi, A. Tanaka, F. Urase, Y. Maeda, H. Ohtani and T. Iwasaka.The effects of pitavastatin, eicosapentaenoic acid and combined therapy on platelet-derived microparticles and adiponectin in hyperlipidemic, diabetic patients. Platelets 2009: 16-22

J. Strony, R. Hoffman, M. Hanson and E. Veltri.Tolerability and effects on lipids of ezetimibe coadministered with pravastatin or simvastatin for twelve months: results from two open-label extension studies in hypercholesterolemic patients. Clin Ther 2008: 2280-97

J. L. Fleg, M. Mete, B. V. Howard, J. G. Umans, M. J. Roman, R. E. Ratner, A. Silverman, J. M. Galloway, J. A. Henderson, M. R. Weir, C. Wilson, M. Stylianou and W. J. Howard.Effect of statins alone versus statins plus ezetimibe on carotid atherosclerosis in type 2 diabetes: the SANDS (Stop Atherosclerosis in Native Diabetics Study) trial. J Am Coll Cardiol 2008: 2198-205

M. H. Davidson, N. Abate, C. M. Ballantyne, A. L. Catapano, X. Xu, J. Lin, E. Rosenberg and A. M. Tershakovec.Ezetimibe/simvastatin compared with atorvastatin or rosuvastatin in lowering to specified levels both LDL-C and each of five other emerging risk factors for coronary heart disease: Non-HDL-cholesterol, TC/HDL-C, apolipoprotein B, apo-B/apo-A-I, or C-reactive protein. J Clin Lipidol 2008: 436-46

J. Strony, B. Yang, M. E. Hanson and E. P. Veltri.Long-term safety and tolerability of ezetimibe coadministered with simvastatin in hypercholesterolemic patients: a randomized, 12-month double-blind extension study. Curr Med Res Opin 2008: 3149-57

P. E. Westerweel, F. L. Visseren, G. R. Hajer, J. K. Olijhoek, I. E. Hoefer, P. de Bree, S. Rafii, P. A. Doevendans and M. C. Verhaar.Endothelial progenitor cell levels in obese men with the metabolic syndrome and the effect of simvastatin monotherapy vs. simvastatin/ezetimibe combination therapy. Eur Heart J 2008: 2808-17

I. R. Hamilton-Craig.After ENHANCE: the cholesterol hypothesis is alive and well. Med J Aust 2008: 303-4

H. N. Ginsberg and R. Ramakrishnan.Kinetic studies of the metabolism of rapidly exchangeable apolipoproteins may leave investigators and readers with exchangeable results. Arterioscler Thromb Vasc Biol 2008: 1685-6

B. Liska, A. A. Khattab, L. Herrmann, M. Abdel-Wahab, R. Westphal, R. Tolg, V. Geist and G. Richardt.Simvastatin and ezetimibe in addition to nonpharmacological risk factor modification for achieving new low-density lipoprotein cholesterol targets. Herz 2008: 362-7

J. K. Olijhoek, G. R. Hajer, Y. van der Graaf, G. M. Dallinga-Thie and F. L. Visseren.The effects of low-dose simvastatin and ezetimibe compared to high-dose simvastatin alone on post-fat load endothelial function in patients with metabolic syndrome: a randomized double-blind crossover trial. J Cardiovasc Pharmacol 2008: 145-50

Y. Saito, M. Yokoyama, H. Origasa, M. Matsuzaki, Y. Matsuzawa, Y. Ishikawa, S. Oikawa, J. Sasaki, H. Hishida, H. Itakura, T. Kita, A. Kitabatake, N. Nakaya, T. Sakata, K. Shimada and K. Shirato.Effects of EPA on coronary artery disease in hypercholesterolemic patients with multiple risk factors: sub-analysis of primary prevention cases from the Japan EPA Lipid Intervention Study (JELIS). Atherosclerosis 2008: 135-40

K. Tanaka, Y. Ishikawa, M. Yokoyama, H. Origasa, M. Matsuzaki, Y. Saito, Y. Matsuzawa, J. Sasaki, S. Oikawa, H. Hishida, H. Itakura, T. Kita, A. Kitabatake, N. Nakaya, T. Sakata, K. Shimada and K. Shirato.Reduction in the recurrence of stroke by eicosapentaenoic acid for hypercholesterolemic patients: subanalysis of the JELIS trial. Stroke 2008: 2052-8

M. Settergren, F. Bohm, L. Ryden and J. Pernow.Cholesterol lowering is more important than pleiotropic effects of statins for endothelial function in patients with dysglycaemia and coronary artery disease. Eur Heart J 2008: 1753-60

I. Avisar, J. G. Brook and E. Wolfovitz.Atorvastatin monotherapy vs. combination therapy in the management of patients with combined hyperlipidemia. Eur J Intern Med 2008: 203-8

.Extended ASCOT - lipid lowering (ASCOT-LLA) study shows positive results of atorvastatin. Cardiovasc J Afr 2008: 49-51

H. T. May, J. L. Anderson, R. R. Pearson, J. R. Jensen, B. D. Horne, F. Lavasani, H. D. Yannicelli and J. B. Muhlestein.Comparison of effects of simvastatin alone versus fenofibrate alone versus simvastatin plus fenofibrate on lipoprotein subparticle profiles in diabetic patients with mixed dyslipidemia (from the Diabetes and Combined Lipid Therapy Regimen study). Am J Cardiol 2008: 486-9

Bays, H. E., Braeckman, R. A., Ballantyne, C. M., Kastelein, J. J., Otvos, J. D., Stirtan, W. G., and Soni, P. N..Icosapent ethyl, a pure EPA omega-3 fatty acid: Effects on lipoprotein particle concentration and size in patients with very high triglyceride levels (the MARINE study). J. Clin. Lipidology 2012 :565-572

McBride, R..Adding niacin to simvastatin did not improve clinical outcomes in patients with CV disease and dyslipidemia. Ann. Intern. Med. 2012 :JC4-8

Karbasi-Afshar, R., Shahmari, A., and Saburi, A..Echocardiographic and exercise test findings in patients with dyslipidemia and coronary artery disease before and after treatment with Simvastatin with or without fenofibrate. Iran. Cardiovasc. Res. J. 2012 :143-147

Toyama, K., Sasaki, O., Nishioka, T., and Ito, H..Beneficial effect of eicosapentaenoic acid on endothelial function in old myocardial infarction patients under adequate statin therapy. J. Am. Coll. Cardiol. 2012 :E1773

Wakita, Y., Wakida, Y., Itou, T., and Mizuno, R..High purity eicosapentaenoic acid in addition to a strong statin makes regression of coronary plaque in patients with angina pectoris. Circulation 2011 :

Insull Jr., W., Toth, P. P., Superko, H. R., Thakkar, R. B., Krause, S., Jiang, P., Parreno, R. A., and Padley, R. J..Combination of niacin extended-release and simvastatin results in a less atherogenic lipid profile than atorvastatin monotherapy. Vasc. Health Risk Manage. 2010 :1065-1075

Cawood, A. L., Ding, R., Napper, F. L., Young, R. H., Williams, J. A., Ward, M. J. A., Gudmundsen, O., Vige, R., Payne, S. P. K., Ye, S., Shearman, C. P., Gallagher, P. J., Grimble, R. F., and Calder, P. C..Eicosapentaenoic acid (EPA) from highly concentrated n-3 fatty acid ethyl esters is incorporated into advanced atherosclerotic plaques and higher plaque EPA is associated with decreased plaque inflammation and increased stability. Atherosclerosis 2010 :252-259

Insull Jr., W., Basile, J. N., Vo, A. N., Jiang, P., Thakkar, R., and Padley, R. J..Efficacy and safety of combination therapy with niacin extended-release and simvastatin versus atorvastatin in patients with dyslipidemia: The SUPREME Study. J. Clin. Lipidology 2009 :109-118

Taylor, A. J. and Stanek, E. J..Flushing and the HDL-C response to extended-release niacin. J. Clin. Lipidology 2008 :285-288

Rodney, R. A., Sugimoto, D., Wagman, B., Zieve, F., Kerzner, B., Strony, J., Yang, B., Suresh, R., and Veltri, E..Efficacy and safety of coadministration of ezetimibe and simvastatin in African-American patients with primary hypercholesterolemia. J Natl Med Assoc 2006 :772-8

Geiss, H. C., Otto, C., and Parhofer, K. G..Effect of ezetimibe on low-density lipoprotein subtype distribution: results of a placebo-controlled, double-blind trial in patients treated by regular low-density lipoprotein apheresis and statins. Metabolism 2006 :599-604

Landray, M., Baigent, C., Leaper, C., Adu, D., Altmann, P., Armitage, J., Ball, S., Baxter, A., Blackwell, L., Cairns, H. S., Carr, S., Collins, R., Kourellias, K., Rogerson, M., Scoble, J. E., Tomson, C. R., Warwick, G., and Wheeler, D. C..The second United Kingdom Heart and Renal Protection (UK-HARP-II) Study: a randomized controlled study of the biochemical safety and efficacy of adding ezetimibe to simvastatin as initial therapy among patients with CKD. Am J Kidney Dis 2006 :385-95

Pearson, T., Denke, M., McBride, P., Battisti, W. P., Brady, W. E., and Palmisano, J..Effectiveness of the addition of ezetimibe to ongoing statin therapy in modifying lipid profiles and attaining low-density lipoprotein cholesterol goals in older and elderly patients: subanalyses of data from a randomized, double-blind, placebo-controlled trial. Am J Geriatr Pharmacother 2005 :218-28

Athyros, V. G., Mikhailidis, D. P., Papageorgiou, A. A., Didangelos, T. P., Peletidou, A., Kleta, D., Karagiannis, A., Kakafika, A. I., Tziomalos, K., and Elisaf, M..Targeting vascular risk in patients with metabolic syndrome but without diabetes. Metabolism 2005 :1065-74

Brohet, C., Banai, S., Alings, A. M., Massaad, R., Davies, M. J., and Allen, C..LDL-C goal attainment with the addition of ezetimibe to ongoing simvastatin treatment in coronary heart disease patients with hypercholesterolemia. Curr Med Res Opin 2005 :571-8

Geiss, H. C., Otto, C., Hund-Wissner, E., and Parhofer, K. G..Effects of ezetimibe on plasma lipoproteins in severely hypercholesterolemic patients treated with regular LDL-apheresis and statins. Atherosclerosis 2005 :107-12

Grundy, S. M., Vega, G. L., Yuan, Z., Battisti, W. P., Brady, W. E., and Palmisano, J..Effectiveness and tolerability of simvastatin plus fenofibrate for combined hyperlipidemia (the SAFARI trial). Am J Cardiol 2005 :462-8

Ballantyne, C. M., Miller, E., and Chitra, R..Efficacy and safety of rosuvastatin alone and in combination with cholestyramine in patients with severe hypercholesterolemia: a randomized, open-label, multicenter trial. Clin Ther 2004 :1855-64

Derosa, G., Cicero, A. E., Bertone, G., Piccinni, M. N., Ciccarelli, L., and Roggeri, D. E..Comparison of fluvastatin + fenofibrate combination therapy and fluvastatin monotherapy in the treatment of combined hyperlipidemia, type 2 diabetes mellitus, and coronary heart disease: a 12-month, randomized, double-blind, controlled trial. Clin Ther 2004 :1599-607

Taylor, A. J., Sullenberger, L. E., Lee, H. J., Lee, J. K., and Grace, K. A..Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) 2: a double-blind, placebo-controlled study of extended-release niacin on atherosclerosis progression in secondary prevention patients treated with statins. Circulation 2004 :3512-7

Simons, L., Tonkon, M., Masana, L., Maccubbin, D., Shah, A., Lee, M., and Gumbiner, B..Effects of ezetimibe added to on-going statin therapy on the lipid profile of hypercholesterolemic patients with diabetes mellitus or metabolic syndrome. Curr Med Res Opin 2004 :1437-45

Kosoglou, T., Statkevich, P., Yang, B., Suresh, R., Zhu, Y., Boutros, T., Maxwell, S. E., Tiessen, R., and Cutler, D. L..Pharmacodynamic interaction between ezetimibe and rosuvastatin. Curr Med Res Opin 2004 :1185-95

Ballantyne, C. M., Lipka, L. J., Sager, P. T., Strony, J., Alizadeh, J., Suresh, R., and Veltri, E. P..Long-term safety and tolerability profile of ezetimibe and atorvastatin coadministration therapy in patients with primary hypercholesterolaemia. Int J Clin Pract 2004 :653-8

Hong, H., Xu, Z. M., Pang, B. S., Cui, L., Wei, Y., Guo, W. J., Mao, Y. L., and Yang, X. C..Effects of simvastain combined with omega-3 fatty acids on high sensitive C-reactive protein, lipidemia, and fibrinolysis in patients with mixed dyslipidemia. Chin Med Sci J 2004 :145-9

Kosoglou, T., Statkevich, P., Meyer, I., Cutler, D. L., Musiol, B., Yang, B., Zhu, Y., Maxwell, S. E., and Veltri, E. P..Effects of ezetimibe on the pharmacodynamics and pharmacokinetics of lovastatin. Curr Med Res Opin 2004 :955-65

Ballantyne, C. M., Blazing, M. A., King, T. R., Brady, W. E., and Palmisano, J..Efficacy and safety of ezetimibe co-administered with simvastatin compared with atorvastatin in adults with hypercholesterolemia. Am J Cardiol 2004 :1487-94

Bays, H. E., Dujovne, C. A., McGovern, M. E., White, T. E., Kashyap, M. L., Hutcheson, A. G., and Crouse, J. R..Comparison of once-daily, niacin extended-release/lovastatin with standard doses of atorvastatin and simvastatin (the ADvicor Versus Other Cholesterol-Modulating Agents Trial Evaluation. Am J Cardiol 2003 :667-72

Sager, P. T., Melani, L., Lipka, L., Strony, J., Yang, B., Suresh, R., and Veltri, E..Effect of coadministration of ezetimibe and simvastatin on high-sensitivity C-reactive protein. Am J Cardiol 2003 :1414-8

Nordoy, A., Svensson, B., and Hansen, J. B..Atorvastatin and omega-3 fatty acids protect against activation of the coagulation system in patients with combined hyperlipemia. J Thromb Haemost 2003 :690-7

Gagne, C., Bays, H. E., Weiss, S. R., Mata, P., Quinto, K., Melino, M., Cho, M., Musliner, T. A., and Gumbiner, B..Efficacy and safety of ezetimibe added to ongoing statin therapy for treatment of patients with primary hypercholesterolemia. Am J Cardiol 2002 :1084-91

Kosoglou, T., Meyer, I., Veltri, E. P., Statkevich, P., Yang, B., Zhu, Y., Mellars, L., Maxwell, S. E., Patrick, J. E., Cutler, D. L., Batra, V. K., and Affrime, M. B..Pharmacodynamic interaction between the new selective cholesterol absorption inhibitor ezetimibe and simvastatin. Br J Clin Pharmacol 2002 :309-19

Chan, D. C., Watts, G. F., Barrett, P. H., Beilin, L. J., Redgrave, T. G., and Mori, T. A..Regulatory effects of HMG CoA reductase inhibitor and fish oils on apolipoprotein B-100 kinetics in insulin-resistant obese male subjects with dyslipidemia. Diabetes 2002 :2377-86

Athyros, V. G., Papageorgiou, A. A., Athyrou, V. V., Demitriadis, D. S., and Kontopoulos, A. G..Atorvastatin and micronized fenofibrate alone and in combination in type 2 diabetes with combined hyperlipidemia. Diabetes Care 2002 :1198-202

Chan, D. C., Watts, G. F., Mori, T. A., Barrett, P. H., Beilin, L. J., and Redgrave, T. G..Factorial study of the effects of atorvastatin and fish oil on dyslipidaemia in visceral obesity. Eur J Clin Invest 2002 :429-36

Chan, D. C., Watts, G. F., Barrett, P. H., Beilin, L. J., and Mori, T. A..Effect of atorvastatin and fish oil on plasma high-sensitivity C-reactive protein concentrations in individuals with visceral obesity. Clin Chem 2002 :877-83

Hunninghake, D., Insull, W. Jr, Toth, P., Davidson, D., Donovan, J. M., and Burke, S. K..Coadministration of colesevelam hydrochloride with atorvastatin lowers LDL cholesterol additively. Atherosclerosis 2001 :407-16

Davidson, M. H., Toth, P., Weiss, S., McKenney, J., Hunninghake, D., Isaacsohn, J., Donovan, J. M., and Burke, S. K..Low-dose combination therapy with colesevelam hydrochloride and lovastatin effectively decreases low-density lipoprotein cholesterol in patients with primary hypercholesterolemia. Clin Cardiol 2001 :467-74

Nordoy, A., Hansen, J. B., Brox, J., and Svensson, B..Effects of atorvastatin and omega-3 fatty acids on LDL subfractions and postprandial hyperlipemia in patients with combined hyperlipemia. Nutr Metab Cardiovasc Dis 2001 :7-16

Durrington, P. N., Bhatnagar, D., Mackness, M. I., Morgan, J., Julier, K., Khan, M. A., and France, M..An omega-3 polyunsaturated fatty acid concentrate administered for one year decreased triglycerides in simvastatin treated patients with coronary heart disease and persisting hypertriglyceridaemia. Heart 2001 :544-8

Nordoy, A., Bonaa, K. H., Sandset, P. M., Hansen, J. B., and Nilsen, H..Effect of omega-3 fatty acids and simvastatin on hemostatic risk factors and postprandial hyperlipemia in patients with combined hyperlipemia. Arterioscler Thromb Vasc Biol 2000 :259-65

Simons, L. A., Sullivan, D., Simons, J., and Celermajer, D. S..Effects of atorvastatin monotherapy and simvastatin plus cholestyramine on arterial endothelial function in patients with severe primary hypercholesterolaemia. Atherosclerosis 98 :197-203

Nordoy, A., Bonaa, K. H., Nilsen, H., Berge, R. K., Hansen, J. B., and Ingebretsen, O. C..Effects of Simvastatin and omega-3 fatty acids on plasma lipoproteins and lipid peroxidation in patients with combined hyperlipidaemia. J Intern Med 98 :163-70

Davidson, M. H., Macariola-Coad, J. R., McDonald, A. M., Maki, K. C., and Hall, H. A..Separate and joint effects of marine oil and simvastatin in patients with combined hyperlipidemia. Am J Cardiol 97 :797-8

Wiklund, O., Bondjers, G., Wright, I., and Camejo, G..Insoluble complex formation between LDL and arterial proteoglycans in relation to serum lipid levels and effects of lipid lowering drugs. Atherosclerosis 96 :57-67

Vanhanen, H. T. and Miettinen, T. A..Cholesterol absorption and synthesis during pravastatin, gemfibrozil and their combination. Atherosclerosis 95 :135-46

O'Keefe, J. H. Jr, Harris, W. S., Nelson, J., and Windsor, S. L..Effects of pravastatin with niacin or magnesium on lipid levels and postprandial lipemia. Am J Cardiol 95 :480-4

Vacek, J. L., Dittmeier, G., Chiarelli, T., White, J., and Bell, H. H..Comparison of lovastatin (20 mg) and nicotinic acid (1.2 g) with either drug alone for type II hyperlipoproteinemia. Am J Cardiol 95 :182-4

Smit, J. W., Jansen, G. H., de Bruin, T. W., and Erkelens, D. W..Treatment of combined hyperlipidemia with fluvastatin and gemfibrozil, alone or in combination, does not induce muscle damage. Am J Cardiol 95 :126A-128A

Wiklund, O., Angelin, B., Bergman, M., Berglund, L., Bondjers, G., Carlsson, A., Linden, T., Miettinen, T., Odman, B., Olofsson, S. O., and et, a. l..Pravastatin and gemfibrozil alone and in combination for the treatment of hypercholesterolemia. Am J Med 93 :13-20

O'Brien, R. C., Simons, L. A., Clifton, P., Cooper, M. E., Jennings, G. L., Jerums, G., Nestel, P. J., and Sullivan, D..Comparison of simvastatin and cholestyramine in the treatment of primary hypercholesterolaemia. Med J Aust 90 :480-3

Liu M, Wallmon A Wallin R et al.Effects of stable fish oil and simvastatin on plasma lipoproteins in patients with hyperlipidemia.. Nutr Res 2003 :1027-34

van Dam M, Kastelein J..Efficacy and tolerability of fluvastatin in a titration dosage regimen in hyperlipidaemic patients: Results of a multicentre phase IV study. Clin Drug Investig 2001 :477-84

Ojala, J. P., Helve, E., Karjalainen, K., Tarkkanen, A., and Tikkanen, M. J..Long-term maintenance of therapeutic response to lovastatin in patients with familial and non-familial hypercholesterolemia: a 3-year follow-up. Atherosclerosis 90 :85-95

Mol, M. J., Stuyt, P. M., Demacker, P. N., and Stalenhoef, A. F..The effects of simvastatin on serum lipoproteins in severe hypercholesterolaemia. Neth J Med 90 :182-90

Blagden, M. D. and Chipperfield, R..Efficacy and safety of ezetimibe co-administered with atorvastatin in untreated patients with primary hypercholesterolaemia and coronary heart disease. Curr Med Res Opin 2007 :767-75

Yokoyama, M., Origasa, H., Matsuzaki, M., Matsuzawa, Y., Saito, Y., Ishikawa, Y., Oikawa, S., Sasaki, J., Hishida, H., Itakura, H., Kita, T., Kitabatake, A., Nakaya, N., Sakata, T., Shimada, K., and Shirato, K..Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. Lancet 2007 :1090-8

Ballantyne, C. M., Weiss, R., Moccetti, T., Vogt, A., Eber, B., Sosef, F., and Duffield, E..Efficacy and safety of rosuvastatin 40 mg alone or in combination with ezetimibe in patients at high risk of cardiovascular disease (results from the EXPLORER study). Am J Cardiol 2007 :673-80

Patel, J. V. and Hughes, E. A..Efficacy, safety and LDL-C goal attainment of ezetimibe 10 mg-simvastatin 20 mg vs. placebo-simvastatin 20 mg in UK-based adults with coronary heart disease and hypercholesterolaemia. Int J Clin Pract 2006 :914-21

Berthold, H. K., Naini, A., Di Mauro, S., Hallikainen, M., Gylling, H., Krone, W., and Gouni-Berthold, I..Effect of ezetimibe and/or simvastatin on coenzyme Q10 levels in plasma: a randomised trial. Drug Saf 2006 :703-12

Denke, M., Pearson, T., McBride, P., Gazzara, R. A., Brady, W. E., and Tershakovec, A. M..Ezetimibe added to ongoing statin therapy improves LDL-C goal attainment and lipid profile in patients with diabetes or metabolic syndrome. Diab Vasc Dis Res 2006 :93-102

Athyros, V. G., Mikhailidis, D. P., Didangelos, T. P., Giouleme, O. I., Liberopoulos, E. N., Karagiannis, A., Kakafika, A. I., Tziomalos, K., Burroughs, A. K., and Elisaf, M. S..Effect of multifactorial treatment on non-alcoholic fatty liver disease in metabolic syndrome: a randomised study. Curr Med Res Opin 2006 :873-83

Muhlestein, J. B., May, H. T., Jensen, J. R., Horne, B. D., Lanman, R. B., Lavasani, F., Wolfert, R. L., Pearson, R. R., Yannicelli, H. D., and Anderson, J. L..The reduction of inflammatory biomarkers by statin, fibrate, and combination therapy among diabetic patients with mixed dyslipidemia: the DIACOR (Diabetes and Combined Lipid Therapy Regimen) study. J Am Coll Cardiol 2006 :396-401

Pearson, T. A., Denke, M. A., McBride, P. E., Battisti, W. P., Gazzara, R. A., Brady, W. E., and Palmisano, J..Effectiveness of ezetimibe added to ongoing statin therapy in modifying lipid profiles and low-density lipoprotein cholesterol goal attainment in patients of different races and ethnicities: a substudy of the Ezetimibe add-on to statin for effectiveness trial. Mayo Clin Proc 2006 :1177-85

Davidson, M. H., Stein, E. A., Bays, H. E., Maki, K. C., Doyle, R. T., Shalwitz, R. A., Ballantyne, C. M., and Ginsberg, H. N..Efficacy and tolerability of adding prescription omega-3 fatty acids 4 g/d to simvastatin 40 mg/d in hypertriglyceridemic patients: an 8-week, randomized, double-blind, placebo-controlled study. Clin Ther 2007 :1354-67

Chenot, F., Montant, P. F., Marcovitch, O., Blaimont, M., de Meester, A., and Descamps, O. S..Co-administration of ezetimibe and simvastatin in acute myocardial infarction. Eur J Clin Invest 2007 :357-63

Meyer, B. J., Hammervold, T., Rustan, A. C., and Howe, P. R..Dose-dependent effects of docosahexaenoic acid supplementation on blood lipids in statin-treated hyperlipidaemic subjects. Lipids 2007 :109-15

Bays, H. E. and McGovern, M. E..Time as a variable with niacin extended-release/lovastatin vs. atorvastatin and simvastatin. Prev Cardiol 2005 :226-33

Shankar, P. K., Bhat, R., Prabhu, M., Reddy, B. P., Reddy, M. S., and Reddy, M..Efficacy and tolerability of fixed-dose combination of simvastatin plus ezetimibe in patients with primary hypercholesterolemia: Results of a multicentric trial from India. J Clin Lipidol 2007 :264-70

Kuvin, J. T., Dave, D. M., Sliney, K. A., Mooney, P., Patel, A. R., Kimmelstiel, C. D., and Karas, R. H..Effects of extended-release niacin on lipoprotein particle size, distribution, and inflammatory markers in patients with coronary artery disease. Am J Cardiol 2006 :743-5

Napoli, C., Lepore, S., Chiariello, P., Condorelli, M., and Chiariello, M..Long-term Treatment With Pravastatin Alone and in Combination With Gemfibrozil in Familial Type IIB Hyperlipoproteinemia or Combined Hyperlipidemia. J Cardiovasc Pharmacol Ther 97 :17-26

Kastelein, J. J., Akdim, F., Stroes, E. S., Zwinderman, A. H., Bots, M. L., Stalenhoef, A. F., Visseren, F. L., Sijbrands, E. J., Trip, M. D., Stein, E. A., Gaudet, D., Duivenvoorden, R., Veltri, E. P., Marais, A. D., and de Groot, E..Simvastatin with or without ezetimibe in familial hypercholesterolemia. N Engl J Med 2008 :1431-43

Stein, E. A., Davidson, M. H., Dujovne, C. A., Hunninghake, D. B., Goldberg, R. B., Illingworth, D. R., Knopp, R. H., Miller, V. T., Frost, P., Isaacsohn, J. L., Mitchel, Y. B., Melino, M. R., Shapiro, D., and Tobert, J. A..Efficacy and Tolerability of Low-dose Simvastatin and Niacin, Alone and in Combination, in Patients With Combined Hyperlipidemia: A Prospective Trial. J Cardiovasc Pharmacol Ther 96 :107-116

Stein, E. A., Ballantyne, C. M., Windler, E., Sirnes, P. A., Sussekov, A., Yigit, Z., Seper, C., and Gimpelewicz, C. R..Efficacy and tolerability of fluvastatin XL 80 mg alone, ezetimibe alone, and the combination of fluvastatin XL 80 mg with ezetimibe in patients with a history of muscle-related side effects with other statins. Am J Cardiol 2008 :490-6

Heinonen, T. M., Schrott, H., McKenney, J. M., Sniderman, A. D., Broyles, F. E., Zavoral, J. H., Kivel, F., and Black, D. M..Atorvastatin, a New HMG-CoA Reductase Inhibitor as Monotherapy and Combined With Colestipol. J Cardiovasc Pharmacol Ther 96 :117-122

Tanaka, K., Ishikawa, Y., Yokoyama, M., Origasa, H., Matsuzaki, M., Saito, Y., Matsuzawa, Y., Sasaki, J., Oikawa, S., Hishida, H., Itakura, H., Kita, T., Kitabatake, A., Nakaya, N., Sakata, T., Shimada, K., and Shirato, K..Reduction in the recurrence of stroke by eicosapentaenoic acid for hypercholesterolemic patients: subanalysis of the JELIS trial. Stroke 2008 :2052-8

Ballantyne, C. M., Davidson, M. H., McKenney, J., Keller, L. H., Bajorunas, D. R., and Karas, R. H..Comparison of the safety and efficacy of a combination tablet of niacin extended release and simvastatin vs simvastatin monotherapy in patients with increased non-HDL cholesterol (from the SEACOAST I study). Am J Cardiol 2008 :1428-36

Turk, T. R., Voropaeva, E., Kohnle, M., Nurnberger, J., Philipp, T., Kribben, A., Heemann, U., and Witzke, O..Ezetimibe treatment in hypercholesterolemic kidney transplant patients is safe and effective and reduces the decline of renal allograft function: a pilot study. Nephrol Dial Transplant 2008 :369-73

Gouni-Berthold, I., Berthold, H. K., Gylling, H., Hallikainen, M., Giannakidou, E., Stier, S., Ko, Y., Patel, D., Soutar, A. K., Seedorf, U., Mantzoros, C. S., Plat, J., and Krone, W..Effects of ezetimibe and/or simvastatin on LDL receptor protein expression and on LDL receptor and

HMG-CoA reductase gene expression: a randomized trial in healthy men. Atherosclerosis 2008 :198-207

Ose, L., Johnson-Levonas, A., Reyes, R., Lin, J., Shah, A., Tribble, D., and Musliner, T..A multi-centre, randomised, double-blind 14-week extension study examining the long-term safety and efficacy profile of the ezetimibe/simvastatin combination tablet. Int J Clin Pract 2007 :1469-80

Moore, A., Phan, B. A., Challender, C., Williamson, J., Marcovina, S., and Zhao, X. Q..Effects of adding extended-release niacin and colesevelam to statin therapy on lipid levels in subjects with atherosclerotic disease. J Clin Lipidol 2007 :620-5

Taylor, A. J., Zhu, D., Sullenberger, L. E., Lee, H. J., Lee, J. K., and Grace, K. A..Relationship between glycemic status and progression of carotid intima-media thickness during treatment with combined statin and extended-release niacin in ARBITER 2. Vasc Health Risk Manag 2007 :159-64

Other

M. Madan, T. Vira, E. Rampakakis, A. Gupta, A. Khithani, L. Balleza, J. Vaillancourt, S. Boukas, J. Sampalis and E. de Carolis.A Randomized Trial Assessing the Effectiveness of Ezetimibe in South Asian Canadians with Coronary Artery Disease or Diabetes: The INFINITY Study. Adv Prev Med 2012: 103728

M. Florentin, E. N. Liberopoulos, C. V. Rizos, A. A. Kei, G. Liamis, M. S. Kostapanos and M. S. Elisaf.Colesevelam Plus Rosuvastatin 5 mg/Day Versus Rosuvastatin 10 mg/Day Alone on Markers of Insulin Resistance in Patients with Hypercholesterolemia and Impaired Fasting Glucose. Metab Syndr Relat Disord 2012:

A. P. Agouridis, M. S. Kostapanos, V. Tsimihodimos, C. Kostara, D. P. Mikhailidis, E. T. Bairaktari, A. D. Tselepis and M. S. Elisaf.Effect of rosuvastatin monotherapy or in combination with fenofibrate or omega-3 fatty acids on lipoprotein subfraction profile in patients with mixed dyslipidaemia and metabolic syndrome. Int J Clin Pract 2012: 843-53

L. Ma, C. M. Ballantyne, J. W. Belmont, A. Keinan and A. Brautbar.Interaction between SNPs in the RXRA and near ANGPTL3 gene region inhibits apoB reduction after statin-fenofibric acid therapy in individuals with mixed dyslipidemia. J Lipid Res 2012: 2425-8

K. Okada, N. Iwahashi, T. Endo, H. Himeno, K. Fukui, S. Kobayashi, M. Shimizu, Y. Iwasawa, Y. Morita, A. Wada, T. Shigemasa, Y. Mochida, T. Shimizu, R. Sawada, K. Uchino, S. Umemura and K. Kimura.Long-term effects of ezetimibe-plus-statin therapy on low-density lipoprotein cholesterol levels as compared with double-dose statin therapy in patients with coronary artery disease. Atherosclerosis 2012: 454-6

J. Sasaki, T. Otonari, Y. Sawayama, S. Hata, Y. Oshima, T. Saikawa, S. Biro and S. Kono.Double-dose pravastatin versus add-on ezetimibe with low-dose pravastatin - effects on LDL cholesterol, cholesterol absorption, and cholesterol synthesis in Japanese patients with hypercholesterolemia (PEAS study). J Atheroscler Thromb 2012: 485-93

A. Zinellu, S. Sotgia, E. Pisanu, G. Loriga, L. Deiana, A. E. Satta and C. Carru.LDL S-homocysteinylation decrease in chronic kidney disease patients undergone lipid lowering therapy. Eur J Pharm Sci 2012: 117-23

C. C. Yu, W. T. Lai, K. C. Shih, T. H. Lin, C. H. Lu, H. J. Lai, M. E. Hanson and J. J. Hwang.Efficacy, safety and tolerability of ongoing statin plus ezetimibe versus doubling the ongoing statin dose in hypercholesterolemic Taiwanese patients: an open-label, randomized clinical trial. BMC Res Notes 2012: 251

A. G. Semb, T. K. Kvien, D. A. DeMicco, R. Fayyad, C. C. Wun, J. C. LaRosa, J. Betteridge, T. R. Pedersen and I. Holme.Effect of intensive lipid-lowering therapy on cardiovascular outcome in patients with and those without inflammatory joint disease. Arthritis Rheum 2012: 2836-46

G. N. Kouvelos, E. M. Arnaoutoglou, M. I. Matsagkas, C. Kostara, C. Gartzonika, E. T. Bairaktari and H. J. Milionis.Effects of rosuvastatin with or without ezetimibe on clinical outcomes in patients undergoing elective vascular surgery: results of a pilot study. J Cardiovasc Pharmacol Ther 2013: 5-12

T. Arimura, S. Miura, A. Ike, M. Sugihara, A. Iwata, H. Nishikawa, A. Kawamura and K. Saku.Comparison of the efficacy and safety of statin and statin/ezetimibe therapy after coronary stent implantation in patients with stable angina. J Cardiol 2012: 111-8

E. Moutzouri, E. N. Liberopoulos, M. Florentin, G. Liamis and M. S. Elisaf.Effects of statin monotherapy versus statin plus ezetimibe combination on serum uric acid levels. J Cardiovasc Pharmacol Ther 2013: 13-8

T. Nakamura, M. Hirano, Y. Kitta, D. Fujioka, Y. Saito, K. Kawabata, J. E. Obata, Y. Watanabe, K. Watanabe and K. Kugiyama.A comparison of the efficacy of combined ezetimibe and statin therapy with doubling of statin dose in patients with remnant lipoproteinemia on previous statin therapy. J Cardiol 2012: 12-7

A. Shekhar Pandey, S. Bissonnette, S. Boukas, E. Rampakakis and J. S. Sampalis.Effectiveness and tolerability of ezetimibe co-administered with statins versus statin dose-doubling in high-risk patients with persistent hyperlipidemia: The EZE(STAT)2 trial. Arch Med Sci 2011: 767-75

Y. Uemura, M. Watarai, H. Ishii, M. Koyasu, K. Takemoto, D. Yoshikawa, R. Shibata, T. Matsubara and T. Murohara.Atorvastatin 10 mg plus ezetimibe 10mg compared with atorvastatin 20 mg: impact on the lipid profile in Japanese patients with abnormal glucose tolerance and coronary artery disease. J Cardiol 2012: 50-6

M. Averna, L. Missault, H. Vaverkova, M. Farnier, M. Viigimaa, Q. Dong, A. Shah, A. O. Johnson-Levonas, W. Taggart and P. Brudi.Lipid-altering efficacy of switching to ezetimibe/simvastatin 10/20 mg versus rosuvastatin 10 mg in high-risk patients with and without metabolic syndrome. Diab Vasc Dis Res 2011: 262-70

S. C. Ramos, F. A. Fonseca, S. H. Kasmas, F. T. Moreira, T. Helfenstein, N. C. Borges, R. A. Moreno, V. M. Rezende, F. C. Silva and M. C. Izar.The role of soluble fiber intake in patients under highly effective lipid-lowering therapy. Nutr J 2011: 80

M. Viigimaa, H. Vaverkova, M. Farnier, M. Averna, L. Missault, M. E. Hanson, Q. Dong, A. Shah and P. Brudi.Ezetimibe/simvastatin 10/20 mg versus rosuvastatin 10 mg in high-risk hypercholesterolemic patients stratified by prior statin treatment potency. Lipids Health Dis 2010: 127

H. Vaverkova, M. Farnier, M. Averna, L. Missault, M. Viigimaa, Q. Dong, A. Shah, A. O. Johnson-Levonas and P. Brudi.Lipid-altering efficacy of ezetimibe/simvastatin 10/20 mg compared to rosuvastatin 10 mg in high-risk patients with and without type 2 diabetes mellitus inadequately controlled despite prior statin monotherapy. Cardiovasc Ther 2012: 61-74

H. E. Bays, K. C. Maki, J. McKenney, R. Snipes, A. Meadowcroft, R. Schroyer, R. T. Doyle and E. Stein.Long-term up to 24-month efficacy and safety of concomitant prescription omega-3-acid ethyl esters and simvastatin in hypertriglyceridemic patients. Curr Med Res Opin 2010: 907-15

S. Conard, H. Bays, L. A. Leiter, S. Bird, J. Lin, M. E. Hanson, A. Shah and A. M. Tershakovec.Ezetimibe added to atorvastatin compared with doubling the atorvastatin dose in patients at high risk for coronary heart disease with diabetes mellitus, metabolic syndrome or neither. Diabetes Obes Metab 2010: 210-8

R. B. Goldberg, J. R. Guyton, T. Mazzone, R. S. Weinstock, A. B. Polis, D. Tipping, J. E. Tomassini and A. M. Tershakovec.Relationships between metabolic syndrome and other baseline factors and the efficacy of ezetimibe/simvastatin and atorvastatin in patients with type 2 diabetes and hypercholesterolemia. Diabetes Care 2010: 1021-4

S. S. Kumar, K. A. Lahey, A. Day and S. A. LaHaye.Comparison of the efficacy of administering a combination of ezetimibe plus fenofibrate versus atorvastatin monotherapy in the treatment of dyslipidemia. Lipids Health Dis 2009: 56

L. Jakulj, M. N. Vissers, A. K. Groen, B. A. Hutten, D. Lutjohann, E. P. Veltri and J. J. Kastelein.Baseline cholesterol absorption and the response to ezetimibe/simvastatin therapy: a post-hoc analysis of the ENHANCE trial. J Lipid Res 2010: 755-62

Z. C. Sang, F. Wang, Q. Zhou, Y. H. Li, Y. G. Li, H. P. Wang and S. Y. Chen.Combined use of extended-release niacin and atorvastatin: safety and effects on lipid modification. Chin Med J (Engl) 2009: 1615-20

T. Nakamura, E. Sato, N. Fujiwara, Y. Kawagoe, Y. Ueda, T. Suzuki, S. Ueda, K. Fukami, S. Okuda and S. Yamagishi.Co-administration of ezetimibe enhances proteinuria-lowering effects of pitavastatin in chronic kidney disease patients partly via a cholesterol-independent manner. Pharmacol Res 2010: 58-61

G. Derosa, P. Maffioli, S. A. Salvadeo, I. Ferrari, A. Gravina, R. Mereu, I. Palumbo, A. D'Angelo and A. F. Cicero.Fenofibrate, simvastatin and their combination in the management of dyslipidaemia in type 2 diabetic patients. Curr Med Res Opin 2009: 1973-83

A. Meaney, G. Ceballos, J. Asbun, G. Solache, E. Mendoza, A. Vela and E. Meaney.The VYtorin on Carotid intima-media thickness and overall arterial rigidity (VYCTOR) study. J Clin Pharmacol 2009: 838-47

K. Winkler, T. Schewe, G. Putz, N. Odunc, G. Schafer, E. Siegel, U. Geisen, C. Abletshauser and M. M. Hoffmann.Fluvastatin/fenofibrate vs. simvastatin/ezetimibe in patients with metabolic syndrome: different effects on LDL-profiles. Eur J Clin Invest 2009: 463-70

T. Sudhop, M. Reber, D. Tribble, A. Sapre, W. Taggart, P. Gibbons, T. Musliner, K. von Bergmann and D. Lutjohann.Changes in cholesterol absorption and cholesterol synthesis caused by ezetimibe and/or simvastatin in men. J Lipid Res 2009: 2117-23

M. J. Zema.Add-on therapy for hypercholesterolemia: a pilot comparison of two gastrointestinally-acting agents in statin-treated patients. J Clin Lipidol 2009: 119-24

A. C. Goldberg, H. E. Bays, C. M. Ballantyne, M. T. Kelly, S. M. Buttler, C. M. Setze, D. J. Sleep and J. C. Stolzenbach.Efficacy and safety of ABT-335 (fenofibric acid) in combination with atorvastatin in patients with mixed dyslipidemia. Am J Cardiol 2009: 515-22

K. C. Maki, B. C. Lubin, M. S. Reeves, M. R. Dicklin and W. S. Harris.Prescription omega-3 acid ethyl esters plus simvastatin 20 and 80 mg: effects in mixed dyslipidemia. J Clin Lipidol 2009: 33-8

P. Brudi, J. P. Reckless, D. P. Henry, T. Pomykaj, S. T. Lim, R. Massaad, K. Vandormael and A. O. Johnson-Levonas.Efficacy of ezetimibe/simvastatin 10/40 mg compared to doubling the dose of low-, medium- and high-potency statin monotherapy in patients with a recent coronary event. Cardiology 2009: 89-97

I. R. Hamilton-Craig.After ENHANCE: the cholesterol hypothesis is alive and well. Med J Aust 2008: 303-4

D. Poldermans, M. Dunkelgrun, O. Schouten and U. Hostalek.Prolonged-release nicotinic acid in patients with atherosclerotic disease in the Netherlands. Eur Surg Res 2008: 313-8

H. Bays, A. Sapre, W. Taggart, J. Liu, R. Capece and A. Tershakovec.Long-term (48-week) safety of ezetimibe 10 mg/day coadministered with simvastatin compared to simvastatin alone in patients with primary hypercholesterolemia. Curr Med Res Opin 2008: 2953-66

I. Avisar, J. G. Brook and E. Wolfovitz.Atorvastatin monotherapy vs. combination therapy in the management of patients with combined hyperlipidemia. Eur J Intern Med 2008: 203-8

J. P. Reckless, P. Henry, T. Pomykaj, S. T. Lim, R. Massaad, K. Vandormael, A. O. Johnson-Levonas, K. Lis, P. Brudi and C. Allen.Lipid-altering efficacy of ezetimibe/simvastatin 10/40 mg compared with doubling the statin dose in patients admitted to the hospital for a recent coronary event: the INFORCE study. Int J Clin Pract 2008: 539-54

R. S. Weinstock, R. B. Goldberg, J. R. Guyton, T. Mazzone, A. Polis, J. E. Tomassini, J. Lin, A. Shah and A. M. Tershakovec.Effect of ezetimibe/simvastatin vs atorvastatin on lowering levels of LDL-C and non-HDL-C, ApoB, and hs-CRP in patients with type 2 diabetes. J Clin Lipidol 2008: 25-35

G. Assmann, F. Kannenberg, D. R. Ramey, T. A. Musliner, S. W. Gutkin and E. P. Veltri.Effects of ezetimibe, simvastatin, atorvastatin, and ezetimibe-statin therapies on non-cholesterol sterols in patients with primary hypercholesterolemia. Curr Med Res Opin 2008: 249-59

Harikrishnan, S., Rajeev, E., Tharakan, J. A., Titus, T., Ajit Kumar, V. K., Sivasankaran, S., Krishnamoorthy, K. M., and Nair, K..Efficacy and safety of combination of extended release niacin and atorvastatin in patients with low levels of high density lipoprotein cholesterol. Indian Heart J. 2008 :215-222

Rodney, R. A., Sugimoto, D., Wagman, B., Zieve, F., Kerzner, B., Strony, J., Yang, B., Suresh, R., and Veltri, E..Efficacy and safety of coadministration of ezetimibe and simvastatin in African-American patients with primary hypercholesterolemia. J Natl Med Assoc 2006 :772-8

Landray, M., Baigent, C., Leaper, C., Adu, D., Altmann, P., Armitage, J., Ball, S., Baxter, A., Blackwell, L., Cairns, H. S., Carr, S., Collins, R., Kourellias, K., Rogerson, M., Scoble, J. E., Tomson, C. R., Warwick, G., and Wheeler, D. C..The second United Kingdom Heart and Renal Protection (UK-HARP-II) Study: a randomized controlled study of the biochemical safety and efficacy of adding ezetimibe to simvastatin as initial therapy among patients with CKD. Am J Kidney Dis 2006 :385-95

Farnier, M., Volpe, M., Massaad, R., Davies, M. J., and Allen, C..Effect of co-administering ezetimibe with on-going simvastatin treatment on LDL-C goal attainment in hypercholesterolemic patients with coronary heart disease. Int J Cardiol 2005 :327-32

Cruz-Fernandez, J. M., Bedarida, G. V., Adgey, J., Allen, C., Johnson-Levonas, A. O., and Massaad, R..Efficacy and safety of ezetimibe co-administered with ongoing atorvastatin therapy in achieving low-density lipoprotein goal in patients with hypercholesterolemia and coronary heart disease. Int J Clin Pract 2005 :619-27

Brohet, C., Banai, S., Alings, A. M., Massaad, R., Davies, M. J., and Allen, C..LDL-C goal attainment with the addition of ezetimibe to ongoing simvastatin treatment in coronary heart disease patients with hypercholesterolemia. Curr Med Res Opin 2005 :571-8

Pearson, T. A., Denke, M. A., McBride, P. E., Battisti, W. P., Brady, W. E., and Palmisano, J..A community-based, randomized trial of ezetimibe added to statin therapy to attain NCEP ATP III goals for LDL cholesterol in hypercholesterolemic patients: the ezetimibe add-on to statin for effectiveness (EASE) trial. Mayo Clin Proc 2005 :587-95

Masana, L., Mata, P., Gagne, C., Sirah, W., Cho, M., Johnson-Levonas, A. O., Meehan, A., Troxell, J. K., and Gumbiner, B..Long-term safety and, tolerability profiles and lipid-modifying efficacy of ezetimibe coadministered with ongoing simvastatin treatment: a multicenter, randomized, double-blind, placebo-controlled, 48-week extension study. Clin Ther 2005 :174-84

Grundy, S. M., Vega, G. L., Yuan, Z., Battisti, W. P., Brady, W. E., and Palmisano, J..Effectiveness and tolerability of simvastatin plus fenofibrate for combined hyperlipidemia (the SAFARI trial). Am J Cardiol 2005 :462-8

Taylor, A. J., Sullenberger, L. E., Lee, H. J., Lee, J. K., and Grace, K. A..Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) 2: a double-blind, placebo-controlled study of extended-release niacin on atherosclerosis progression in secondary prevention patients treated with statins. Circulation 2004 :3512-7

Capuzzi, D. M., Morgan, J. M., Carey, C. M., Intenzo, C., Tulenko, T., Kearney, D., Walker, K., and Cressman, M. D..Rosuvastatin alone or with extended-release niacin: a new therapeutic option for patients with combined hyperlipidemia. Prev Cardiol 2004 :176-81

Kosoglou, T., Statkevich, P., Yang, B., Suresh, R., Zhu, Y., Boutros, T., Maxwell, S. E., Tiessen, R., and Cutler, D. L..Pharmacodynamic interaction between ezetimibe and rosuvastatin. Curr Med Res Opin 2004 :1185-95

Ballantyne, C. M., Lipka, L. J., Sager, P. T., Strony, J., Alizadeh, J., Suresh, R., and Veltri, E. P..Long-term safety and tolerability profile of ezetimibe and atorvastatin coadministration therapy in patients with primary hypercholesterolaemia. Int J Clin Pract 2004 :653-8

Ballantyne, C. M., Blazing, M. A., King, T. R., Brady, W. E., and Palmisano, J..Efficacy and safety of ezetimibe co-administered with simvastatin compared with atorvastatin in adults with hypercholesterolemia. Am J Cardiol 2004 :1487-94

Durrington, P. N., Tuomilehto, J., Hamann, A., Kallend, D., and Smith, K..Rosuvastatin and fenofibrate alone and in combination in type 2 diabetes patients with combined hyperlipidaemia. Diabetes Res Clin Pract 2004 :137-51

Melani, L., Mills, R., Hassman, D., Lipetz, R., Lipka, L., LeBeaut, A., Suresh, R., Mukhopadhyay, P., and Veltri, E..Efficacy and safety of ezetimibe coadministered with pravastatin in patients with primary hypercholesterolemia: a prospective, randomized, double-blind trial. Eur Heart J 2003 :717-28

Gagne, C., Bays, H. E., Weiss, S. R., Mata, P., Quinto, K., Melino, M., Cho, M., Musliner, T. A., and Gumbiner, B..Efficacy and safety of ezetimibe added to ongoing statin therapy for treatment of patients with primary hypercholesterolemia. Am J Cardiol 2002 :1084-91

Chan, D. C., Watts, G. F., Barrett, P. H., Beilin, L. J., Redgrave, T. G., and Mori, T. A..Regulatory effects of HMG CoA reductase inhibitor and fish oils on apolipoprotein B-100 kinetics in insulin-resistant obese male subjects with dyslipidemia. Diabetes 2002 :2377-86

Athyros, V. G., Papageorgiou, A. A., Athyrou, V. V., Demitriadis, D. S., and Kontopoulos, A. G..Atorvastatin and micronized fenofibrate alone and in combination in type 2 diabetes with combined hyperlipidemia. Diabetes Care 2002 :1198-202

Chan, D. C., Watts, G. F., Mori, T. A., Barrett, P. H., Beilin, L. J., and Redgrave, T. G..Factorial study of the effects of atorvastatin and fish oil on dyslipidaemia in visceral obesity. Eur J Clin Invest 2002 :429-36

Gagne, C., Gaudet, D., and Bruckert, E..Efficacy and safety of ezetimibe coadministered with atorvastatin or simvastatin in patients with homozygous familial hypercholesterolemia. Circulation 2002 :2469-75

Chan, D. C., Watts, G. F., Barrett, P. H., Beilin, L. J., and Mori, T. A..Effect of atorvastatin and fish oil on plasma high-sensitivity C-reactive protein concentrations in individuals with visceral obesity. Clin Chem 2002 :877-83

Davidson, M. H., Toth, P., Weiss, S., McKenney, J., Hunninghake, D., Isaacsohn, J., Donovan, J. M., and Burke, S. K..Low-dose combination therapy with colesevelam hydrochloride and lovastatin effectively decreases low-density lipoprotein cholesterol in patients with primary hypercholesterolemia. Clin Cardiol 2001 :467-74

Nordoy, A., Hansen, J. B., Brox, J., and Svensson, B..Effects of atorvastatin and omega-3 fatty acids on LDL subfractions and postprandial hyperlipemia in patients with combined hyperlipemia. Nutr Metab Cardiovasc Dis 2001 :7-16

Durrington, P. N., Bhatnagar, D., Mackness, M. I., Morgan, J., Julier, K., Khan, M. A., and France, M..An omega-3 polyunsaturated fatty acid concentrate administered for one year decreased triglycerides in simvastatin treated patients with coronary heart disease and persisting hypertriglyceridaemia. Heart 2001 :544-8

Simons, L. A..Comparison of atorvastatin alone versus simvastatin +/- cholestyramine in the management of severe primary hypercholesterolaemia (the six cities study). Aust N Z J Med 98 :327-33

Eriksson, M., Hadell, K., Holme, I., Walldius, G., and Kjellstrom, T..Compliance with and efficacy of treatment with pravastatin and cholestyramine: a randomized study on lipid-lowering in primary care. J Intern Med 98 :373-80

Simons, L. A., Sullivan, D., Simons, J., and Celermajer, D. S..Effects of atorvastatin monotherapy and simvastatin plus cholestyramine on arterial endothelial function in patients with severe primary hypercholesterolaemia. Atherosclerosis 98 :197-203

Nordoy, A., Bonaa, K. H., Nilsen, H., Berge, R. K., Hansen, J. B., and Ingebretsen, O. C..Effects of Simvastatin and omega-3 fatty acids on plasma lipoproteins and lipid peroxidation in patients with combined hyperlipidaemia. J Intern Med 98 :163-70

Ito, M. K. and Shabetai, R..Pravastatin alone and in combination with low-dose cholestyramine in patients with primary hypercholesterolemia and coronary artery disease. Am J Cardiol 97 :799-802

Davidson, M. H., Macariola-Coad, J. R., McDonald, A. M., Maki, K. C., and Hall, H. A..Separate and joint effects of marine oil and simvastatin in patients with combined hyperlipidemia. Am J Cardiol 97 :797-8

Gardner, S. F., Schneider, E. F., Granberry, M. C., and Carter, I. R..Combination therapy with low-dose lovastatin and niacin is as effective as higher-dose lovastatin. Pharmacotherapy 96 :419-23

Vanhanen, H. T. and Miettinen, T. A..Cholesterol absorption and synthesis during pravastatin, gemfibrozil and their combination. Atherosclerosis 95 :135-46

O'Keefe, J. H. Jr, Harris, W. S., Nelson, J., and Windsor, S. L..Effects of pravastatin with niacin or magnesium on lipid levels and postprandial lipemia. Am J Cardiol 95 :480-4

Sprecher, D. L., Abrams, J., Allen, J. W., Keane, W. F., Chrysant, S. G., Ginsberg, H., Fischer, J. J., Johnson, B. F., Theroux, P., and Jokubaitis, L..Low-dose combined therapy with fluvastatin and cholestyramine in hyperlipidemic patients. Ann Intern Med 94 :537-43

Simons, L. A., Simons, J., and Parfitt, A..Successful management of primary hypercholesterolaemia with simvastatin and low-dose colestipol. Med J Aust 92 :455-9

O'Brien, R. C., Simons, L. A., Clifton, P., Cooper, M. E., Jennings, G. L., Jerums, G., Nestel, P. J., and Sullivan, D..Comparison of simvastatin and cholestyramine in the treatment of primary hypercholesterolaemia. Med J Aust 90 :480-3

Blagden, M. D. and Chipperfield, R..Efficacy and safety of ezetimibe co-administered with atorvastatin in untreated patients with primary hypercholesterolaemia and coronary heart disease. Curr Med Res Opin 2007 :767-75

Yokoyama, M., Origasa, H., Matsuzaki, M., Matsuzawa, Y., Saito, Y., Ishikawa, Y., Oikawa, S., Sasaki, J., Hishida, H., Itakura, H., Kita, T., Kitabatake, A., Nakaya, N., Sakata, T., Shimada, K., and Shirato, K..Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. Lancet 2007 :1090-8

Ballantyne, C. M., Weiss, R., Moccetti, T., Vogt, A., Eber, B., Sosef, F., and Duffield, E..Efficacy and safety of rosuvastatin 40 mg alone or in combination with ezetimibe in patients at high risk of cardiovascular disease (results from the EXPLORER study). Am J Cardiol 2007 :673-80

Berthold, H. K., Naini, A., Di Mauro, S., Hallikainen, M., Gylling, H., Krone, W., and Gouni-Berthold, I..Effect of ezetimibe and/or simvastatin on coenzyme Q10 levels in plasma: a randomised trial. Drug Saf 2006 :703-12

Athyros, V. G., Mikhailidis, D. P., Didangelos, T. P., Giouleme, O. I., Liberopoulos, E. N., Karagiannis, A., Kakafika, A. I., Tziomalos, K., Burroughs, A. K., and Elisaf, M. S..Effect of multifactorial treatment on non-alcoholic fatty liver disease in metabolic syndrome: a randomised study. Curr Med Res Opin 2006 :873-83

Muhlestein, J. B., May, H. T., Jensen, J. R., Horne, B. D., Lanman, R. B., Lavasani, F., Wolfert, R. L., Pearson, R. R., Yannicelli, H. D., and Anderson, J. L..The reduction of inflammatory biomarkers by statin, fibrate, and combination therapy among diabetic patients with mixed dyslipidemia: the DIACOR (Diabetes and Combined Lipid Therapy Regimen) study. J Am Coll Cardiol 2006 :396-401

Chenot, F., Montant, P. F., Marcovitch, O., Blaimont, M., de Meester, A., and Descamps, O. S..Co-administration of ezetimibe and simvastatin in acute myocardial infarction. Eur J Clin Invest 2007 :357-63

Shankar, P. K., Bhat, R., Prabhu, M., Reddy, B. P., Reddy, M. S., and Reddy, M..Efficacy and tolerability of fixed-dose combination of simvastatin plus ezetimibe in patients with primary hypercholesterolemia: Results of a multicentric trial from India. J Clin Lipidol 2007 :264-70

Kuvin, J. T., Dave, D. M., Sliney, K. A., Mooney, P., Patel, A. R., Kimmelstiel, C. D., and Karas, R. H..Effects of extended-release niacin on lipoprotein particle size, distribution, and inflammatory markers in patients with coronary artery disease. Am J Cardiol 2006 :743-5

Isaacsohn, J. L., Bakker-Arkema, R. G., Fayyad, R., Whitcomb, R., and Black, D. M..Atorvastatin, a New HMG-CoA Reductase Inhibitor, Does Not Affect Glucocorticoid Hormones in Patients With Hypercholesterolemia. J Cardiovasc Pharmacol Ther 97 :243-249

Kastelein, J. J., Akdim, F., Stroes, E. S., Zwinderman, A. H., Bots, M. L., Stalenhoef, A. F., Visseren, F. L., Sijbrands, E. J., Trip, M. D., Stein, E. A., Gaudet, D., Duivenvoorden, R., Veltri, E. P., Marais, A. D., and de Groot, E..Simvastatin with or without ezetimibe in familial hypercholesterolemia. N Engl J Med 2008 :1431-43

Stein, E. A., Davidson, M. H., Dujovne, C. A., Hunninghake, D. B., Goldberg, R. B., Illingworth, D. R., Knopp, R. H., Miller, V. T., Frost, P., Isaacsohn, J. L., Mitchel, Y. B., Melino, M. R., Shapiro, D., and Tobert, J. A..Efficacy and Tolerability of Low-dose Simvastatin and Niacin, Alone and in Combination, in Patients With Combined Hyperlipidemia: A Prospective Trial. J Cardiovasc Pharmacol Ther 96 :107-116

Stein, E. A., Ballantyne, C. M., Windler, E., Sirnes, P. A., Sussekov, A., Yigit, Z., Seper, C., and Gimpelewicz, C. R..Efficacy and tolerability of fluvastatin XL 80 mg alone, ezetimibe alone, and the combination of fluvastatin XL 80 mg with ezetimibe in patients with a history of muscle-related side effects with other statins. Am J Cardiol 2008 :490-6

Dagli, N., Yavuzkir, M., and Karaca, I..The effects of high dose pravastatin and low dose pravastatin and ezetimibe combination therapy on lipid, glucose metabolism and inflammation. Inflammation 2007 :230-5

Reckless, J. P., Henry, P., Pomykaj, T., Lim, S. T., Massaad, R., Vandormael, K., Johnson-Levonas, A. O., Lis, K., Brudi, P., and Allen, C..Lipid-altering efficacy of ezetimibe/simvastatin 10/40 mg compared with doubling the statin dose in patients admitted to the hospital for a recent coronary event: the INFORCE study. Int J Clin Pract 2008 :539-54

Turk, T. R., Voropaeva, E., Kohnle, M., Nurnberger, J., Philipp, T., Kribben, A., Heemann, U., and Witzke, O..Ezetimibe treatment in hypercholesterolemic kidney transplant patients is safe and effective and reduces the decline of renal allograft function: a pilot study. Nephrol Dial Transplant 2008 :369-73

Gouni-Berthold, I., Berthold, H. K., Gylling, H., Hallikainen, M., Giannakidou, E., Stier, S., Ko, Y., Patel, D., Soutar, A. K., Seedorf, U., Mantzoros, C. S., Plat, J., and Krone, W..Effects of ezetimibe and/or simvastatin on LDL receptor protein expression and on LDL receptor and HMG-CoA reductase gene expression: a randomized trial in healthy men. Atherosclerosis 2008 :198-207

Moore, A., Phan, B. A., Challender, C., Williamson, J., Marcovina, S., and Zhao, X. Q..Effects of adding extended-release niacin and colesevelam to statin therapy on lipid levels in subjects with atherosclerotic disease. J Clin Lipidol 2007 :620-5

Guyton, J. R., Goldberg, R. B., Mazzone, T., Weinstock, R. S., Polis, A., Rosenberg, E., and Tershakovec, A. M..Lipoprotein and apolipoprotein ratios in the VYTAL trial of ezetimibe/simvastatin compared with atorvastatin in type 2 diabetes. J Clin Lipidol 2008 :19-24

Ballantyne, C. M., Davidson, M. H., McKenney, J. M., Keller, L. H., Bajorunas, D. R., and Karas, R. H..Comparison of the efficacy and safety of a combination tablet of niacin extended-release and simvastatin with simvastatin 80 mg monotherapy: the SEACOAST II (high-dose) study. J Clin Lipidol 2008 :79-90

Conard, S. E., Bays, H. E., Leiter, L. A., Bird, S. R., Rubino, J., Lowe, R. S., Tomassini, J. E., and Tershakovec, A. M..Efficacy and safety of ezetimibe added on to atorvastatin (20 mg) versus uptitration of atorvastatin (to 40 mg) in hypercholesterolemic patients at moderately high risk for coronary heart disease. Am J Cardiol 2008 :1489-94

Leiter, L. A., Bays, H., Conard, S., Bird, S., Rubino, J., Hanson, M. E., Tomassini, J. E., and Tershakovec, A. M..Efficacy and safety of ezetimibe added on to atorvastatin (40 mg) compared with uptitration of atorvastatin (to 80 mg) in hypercholesterolemic patients at high risk of coronary heart disease. Am J Cardiol 2008 :1495-501

Appendix E. Evidence Tables

Evidence Table E1. Study characteristics – bile acid sequestrants

Author, Year Trial #, "Acronym"	Study Design Site(s)	Inclusion Criteria	Participant Use of Lipid Modifying Agents Prior to Trial	Treatment Duration Washout Period Run-In Period	Arm (Potency)	Subgroup Analyses	Pharmaceutical Industry Support Conflict of interest disclosure by author
2009 Studies							
Barbi, 1992[1] Ismail, 1990[2] NR	Parallel Arm RCT Single Center North America	-Patients with an LDL-C > 90th percentile and at least 160 mg/dl -Age 21-70 years -TG<250 mg/dL -No Type I, III, IV, or V hyperlipoproteinemia; no homozygous familial hypercholesterolemia, DM, untreated thyroid or other endocrine diseases; renal or hepatobiliary disease; chronic pancreatitis; collagen-vascular diseases; MI within the past **6** months or clinically significant heart failure; uncontrolled hypertension; history of CVA; serious gastrointestinal disease; obesity greater than 40% above ideal body weight; excessive alcohol consumption; treatment with cortical steroids, estrogens, androgens, lipid-lowering agents, coumarin anticoagulants, theophylline, barbiturates, or aluminum-containing antacids; and any other condition judged to impair the patient's ability to complete the trial.	Lipid modifying therapy discontinued 6-12 weeks before baseline lipid measures. Baseline lipid values reflect dietary changes.	24 weeks 6-12 week drug washout period 8 week dietary run in	Arm 1: (M) PRV 80 mg Arm 2: (L) Cholestyramine 24g + PRV 40mg Arm 3: * Placebo Arm 4: (L)* PRV 40 mg Arm 5: * Cholestyramine 24g	None	Study funded by pharmaceutical companies. NR
Hunningha ke, 2001[3] NR	Parallel Arm RCT Multicenter	-Patients with moderate hypercholesterolemia (LDL cholesterol >=160 mg/dl, triglycerides <=300 mg/dl)	NR	4 weeks NR 4 week dietary run	Arm 1: (H) ATV 80 mg Arm 2: (M) Colsevelam 3.8g	None	Study funded by pharmaceutical companies. Authors have

Author, Year Trial #, "Acronym"	Study Design Site(s)	Inclusion Criteria	Participant Use of Lipid Modifying Agents Prior to Trial	Treatment Duration Washout Period Run-In Period	Arm (Potency)	Subgroup Analyses	Pharmaceutical Industry Support Conflict of interest disclosure by author
	North America	-Age 18 years or older -Agreement maintain their diet and current fiber dose (if used) -Women of childbearing potential had to have a negative pregnancy test and use contraception -Not taking or on stable dose of steroids, thiazide diuretics, or beta-blockers -No history of dysphagia, swallowing or intestinal motility disorders, or any medically unstable condition		in	+ ATV 10mg Arm 3: * Placebo Arm 4: * Colsevelam 3.8g Arm 5: (M)* ATV 10 mg		pharmaceutical company COI disclosures.
Johansson, 1995[4] NR	Parallel Arm RCT Multicenter Europe	-Patients with polygenic hypercholesterolemia with plasma cholesterol of 6.5-10 mmol/l and plasma TGs below 3 mmol/l -No history of major medical events during the last 6 months	NR	12 weeks NR 12 weeks dietary run in	Arm 1: (H) SMV 40 mg Arm 2: (M) Colestipol 5g +SMV 20mg Arm 3: (M) Colestipol 10g + SMV 20mg Arm 4: * Placebo	None	Study funded by pharmaceutical companies. Authors have pharmaceutical company COI disclosures.
Knapp, 2001[5] NR	Parallel Arm RCT Multicenter North America	-Patients with moderate hypercholesterolemia (LDL>=160 mg/dL and triglyceride level <=300 mg/dL) -Not taking lipid-lowering medication -Age 18 years or older -On stable doses of medications that could affect lipid metabolism,	Lipid-modifying agent naïve	6 weeks NR 4 weeks dietary run in	Arm 1: (M) SMV 20 mg Arm 2: (L) Colsevelam 3.8g + SMV 10mg Arm 3: * Placebo	None	Study funded by pharmaceutical companies. Authors have pharmaceutical company COI disclosures.

Author, Year Trial #, "Acronym"	Study Design Site(s)	Inclusion Criteria	Participant Use of Lipid Modifying Agents Prior to Trial	Treatment Duration Washout Period Run-In Period	Arm (Potency)	Subgroup Analyses	Pharmaceutical Industry Support Conflict of interest disclosure by author
		such as steroids, thiazide diuretics, or beta-blockers (if used) -No poorly controlled diabetes/hypertension, real or liver disease, unstable cardiac disease, MI/CABG/ angioplasty within 2 months, pregnant or lactating -No history of dysphagia, swallowing disorders, or intestinal motility disorders, untreated thyroid disease, clinically important liver or renal disease, vasculitis, HIV -Women of child-bearing potential were required to have negative pregnancy tests at screening and to use approved birth control methods -No use of erythromycin, cyclosporine, nefazodone, ketoconazole, and itraconazole			Arm 4: * Colesevelam 3.8g Arm 5: (L)* SMV 10 mg Arm 6: * Colesevelam 2.3 g Arm 7: (M)* Colsevelam 2.3g + SMV 20mg		
Pravastatin Multicenter Study Group II, 1993[6] NR	Parallel Arm RCT Multicenter North America	-Patients with primary hypercholesterolemia (LDL-C >=160 mg/dL and LDL-C greater than the 90^{th} percentile for age and sex in US population -TG level <2.82 mmol/L -No premenopausal women unless surgically sterile a -No patients with non-type II hyperlipoproteinemia, DM, impaired hepatic or renal function, severe or unstable angina, excessive obesity, or uncontrolled	Lipid modifying therapy discontinued 6 weeks before baseline lipid measures	24 weeks 6-12 week drug wash out period 4 weeks dietary run in followed by 3-6 weeks of single-blind placebo run in	Arm 1: (M) PRV 80 mg Arm 2: (L) Cholestyramine 24g + PRV 40mg Arm 3: * Placebo Arm 4: * Cholestyramine	None	Study funded by pharmaceutical companies. NR

Author, Year **Trial #, "Acronym"**	**Study Design** **Site(s)**	**Inclusion Criteria**	**Participant Use of Lipid Modifying Agents Prior to Trial**	**Treatment Duration** **Washout Period** **Run-In Period**	**Arm (Potency)**	**Subgroup Analyses**	**Pharmaceutical Industry Support** **Conflict of interest disclosure by author**
		hypertension. -No patients who consume more than10 alcoholic drinks per week -No patients with hypersensitivity to cholestyramine -No patients receiving corticosteroids, androgens, or estrogens except as continuous, stable replacement. -No patients taking anticoagulants, theophylline, barbiturates, or quinidine or those regularly taking aluminum-containing antacids			24g Arm 5: (L)* PRV 20 mg		
Schrott, 1995[7] NR	Parallel Arm RCT Multicenter North America	Patients with moderate hypercholesterolemia (LDL elevations)	NR	12 weeks NR 6 weeks dietary run in	Arm 1: (M) LOV 40 mg Arm 2: (L) Colestipol 5g +LOV 20mg Arm 3: (L) Colestipol 10g +LOV 20mg Arm 4: * Placebo	None	Study funded by pharmaceutical companies. Authors have pharmaceutical company COI disclosures.

COI conflicts of interest; CVD cardiovascular disease; DM diabetes mellitus; LDL low density lipoprotein; NR not reported; RCT randomized controlled trial; RSV Rosuvastatin; TG triglycerides.
*Arm ineligible for study inclusion.

Evidence Table E2. Baseline population characteristics – bile acid sequestrants

Author, Year	Arm (Potency)	N	Age	Female N (%)	Race N (%)	Smoking Status N (%)	Prior CHD N (%)	Prior CVA N (%)	Prior REVASC N (%)	DM N (%)	LDL	Between Group Differences
2009 Studies												
Barbi, 1992[1] Ismail, 1990[2]	Arm 1: (M) PRV 80 mg Arm 2: (L) Cholestyramine 24g + PRV 40mg Arm 3: * Placebo Arm 4: (L)* PRV 40 mg Arm 5: * Cholestyramine 24g	Arm 1: 9 Arm 2: 9 Arm 3: 7 Arm 4: 8 Arm 5: 7	All: Mean: 57.8 SD: 6.7	All: 2	NR	NR	NR	NR	NR	NR	Arm 1: Mean: 224 mg/dL Arm 2: Mean: 232 mg/dL Arm 3: Mean: 223 mg/dL Arm 4: Mean: 231 mg/dL Arm 5: Mean: 202 mg/dL	NR
Hunninghake, 2001[3]	Arm 1: (H) ATV 80 mg Arm 2: (M) Colsevelam 3.8g + ATV 10mg Arm 3:* Placebo Arm 4:* Colsevelam 3.8g	Arm 1: 20 Arm 2: 19 Arm 3: 19 Arm 4: 17 Arm 5: 19	Arm 1: Mean: 61 SD: 12 Arm 2: Mean: 53 SD: 14 Arm 3: Mean: 57 SD: 8 Arm 4: Mean: 57	Arm 1: 9 (45%) Arm 2: 4 (21%) Arm 3: 4 (21%) Arm 4: 10 (59%) Arm 5: 10 (53%)	NR	NR	NR	NR	NR	NR	Arm 1: Mean: 182 mg/dL SE: 3 Arm 2: Mean: 187 mg/dL SE: 4 Arm 3: Mean: 185 mg/dL SE: 5	NR

Author, Year	Arm (Potency)	N	Age	Female N (%)	Race N (%)	Smoking Status N (%)	Prior CHD N (%)	Prior CVA N (%)	Prior REVASC N (%)	DM N (%)	LDL	Between Group Differences
	Arm 5: (M)* ATV 10 mg		SD: 11 Arm 5: Mean: 58 SD: 12								Arm 4: Mean: 184 mg/dL SE: 5 Arm 5: Mean: 182 mg/dL SE: 6	
Johansson, 1995[4]	Arm 1: (H) SMV 40 mg Arm 2: (M) Colestipol 5g +SMV 20mg Arm 3: (M) Colestipol 10g + SMV 20mg Arm 4: * Placebo	Arm 1: 26 Arm 2: 29 Arm 3: 28 Arm 4: 29	Arm 1: Mean: 53 Arm 2: Mean: 53 Arm 3: Mean: 51 Arm 4: Mean: 53	Arm 1: 10 Arm 2: 5 Arm 3: 4 Arm 4: 5	NR	Current smokers Arm 1: (27%) Arm 2: (24%) Arm 3: (25%) Arm 4: (24%)	NR	NR	NR	NR	Arm 1: Mean: 5.74 mmol/l SD: 0.15 Arm 2: Mean: 5.64 mmol/l SD: 0.15 Arm 3: Mean: 5.79 mmol/l SD: 0.17 Arm 4: Mean: 5.65 mmol/l SD: 0.15	No significant between group differences.
Knapp, 2001[5]	Arm 1: (M) SMV 20 mg Arm 2: (L) Colsevelam 3.8g + SMV 10mg	Arm 1: 39 Arm 2: 34 Arm 3: 33 Arm 4: 37	Arm 1: Mean: 54 SD: 12 Arm 2: Mean: 54 SD: 12	Arm 1: (38%) Arm 2: (38%) Arm 3: (48%)	Arm 1: White: (95%) Black: (5%) Hispanic: (0%) Asian: (0%) Other: (0%)	NR	NR	NR	NR	NR	Arm 1: Mean: 180 mg/dL SD: 23 Arm 2: Mean: 196 mg/dL	No significant between group differences.

Author, Year	Arm (Potency)	N	Age	Female N (%)	Race N (%)	Smoking Status N (%)	Prior CHD N (%)	Prior CVA N (%)	Prior REVASC N (%)	DM N (%)	LDL	Between Group Differences
	Arm 3: * Placebo Arm 4: * Colesevelam 3.8g Arm 5: (L)* SMV 10 mg Arm 6: * Colesevelam 2.3g Arm 7: (M)* Colsevelam 2.3g + SMV 20mg	Arm 5: 35 Arm 6: 36 Arm 7: 37	Arm 3: Mean: 55 SD: 12 Arm 4: Mean: 53 SD: 14 Arm 5: Mean: 56 SD: 12 Arm 6: Mean: 58 SD: 10 Arm 7: Mean: 53 SD: 15	Arm 4: (46%) Arm 5: (54%) Arm 6: (58%) Arm 7: (46%)	Arm 2: White: (97%) Black: (0%) Hispanic: (0%) Asian: (3%) Other: (0%) Arm 3: White: (94%) Black: (3%) Hispanic: (0%) Asian: (3%) Other: (0%) Arm 4: White: (89%) Black:(5%) Hispanic: (3%) Asian: (3%) Other: (0%) Arm 5: White: (91%) Black: (6%) Hispanic: (0%) Asian: (0%) Other: (3%) Arm 6: White: (97%)						SD: 49 Arm 3: Mean: 184 mg/dL SD: 25 Arm 4: Mean: 198 mg/dL SD: 39 Arm 5: Mean: 183 mg/dL SD: 29 Arm 6: Mean: 186 mg/dL SD: 24 Arm 7: Mean: 191 mg/dL SD: 35	

Author, Year	Arm (Potency)	N	Age	Female N (%)	Race N (%)	Smoking Status N (%)	Prior CHD N (%)	Prior CVA N (%)	Prior REVASC N (%)	DM N (%)	LDL	Between Group Differences
					Black: (3%) Hispanic: (0%) Asian: (0%) Other: (0%) Arm 7: White: (97%) Black: (0%) Hispanic: (0%) Asian: (3%) Other: (0%)							
Pravastatin Multicenter Study Group II, 1993[6]	Arm 1: (M) PRV 80 mg Arm 2: (L) Cholestyramine 24g + PRV 40mg Arm 3: * Placebo Arm 4: * Cholestyramine 24g Arm 5: (L)* PRV 20 mg	Arm 1: 63 Arm 2: 64 Arm 3: 60 Arm 4: 61 Arm 5: 63	Arm 1: Mean: 51.6 Arm 2: Mean: 52.8 Arm 3: Mean: 52.8 Arm 4: Mean: 51.4 Arm 5: Mean: 50.8	Arm 1: 18 Arm 2: 19 Arm 3: 23 Arm 4: 19 Arm 5: 16	Arm 1: White: 61 Other: 2 Arm 2: White: 63 Other: 1 Arm 3: White: 58 Other: 2 Arm 4: White: 54 Other: 7 Arm 5: White: 62 Other: 1	NR	NR	NR	NR	NR	Arm 1: Mean: 236 mg/dL SE: 5.4 Arm 2: Mean: 236 mg/dL SE: 5.0 Arm 3: Mean: 232 mg/dL SE: 5.8 Arm 4: Mean: 236 mg/dL SE: 6.6 Arm 5: Mean: 236 mg/dL SE: 5.0	No significant between group differences.

Author, Year	Arm (Potency)	N	Age	Female N (%)	Race N (%)	Smoking Status N (%)	Prior CHD N (%)	Prior CVA N (%)	Prior REVASC N (%)	DM N (%)	LDL	Between Group Differences
Schrott, 1995[7]	Arm 1: (M) LOV 40 mg Arm 2: (L) Colestipol 5g +LOV 20mg Arm 3: (L) Colestipol 10g +LOV 20mg Arm 4: * Placebo	Arm 1: 24 Arm 2: 23 Arm 3: 23 Arm4: 24	Arm 1: Mean: 57 SE: 2.4 Arm 2: Mean: 56 SE: 2.4 Arm 3: Mean: 61 SE: 1.7 Arm 3: Mean: 59 SE: 2.1	Arm 1: 10 Arm 2: 9 Arm 3: 7 Arm 4: 12	NR	Arm 1: (17%) Arm 2: (9%) Arm 3: (4%) Arm4: (17%)	NR	NR	NR	NR	Arm 1: Mean: 195 mg/dL SE: 3.3 Arm 2: Mean: 191 mg/dL SE: 3.3 Arm 3: Mean: 186 mg/dL SE: 3.8 Arm 4: Mean: 185 mg/dL SE: 2.8	No significant between group differences.

NR not reported; RSV Rosuvastatin; SD standard deviation

Evidence Table E3. LDL outcome – bile acid sequestrants

Author, Year	Arm (Potency)	Outcome Units	Baseline N	Baseline Outcome	Timepoint(s)	N at Timepoint(s)	Outcome at Timepoint(s)	Within Arm Comparisons	Between Arm Comparisons
2009 Studies									
Barbi, 1992[1] Ismail, 1990[2]	Arm1: (M) PRV 80 mg	Continuous LDL – calculated mg/dL	9	Mean: 224	8 weeks	9	Mean: 151	Calculated % change from baseline: -33 P<=0.05	
	Arm 2: (L) Cholestyramine 24g + PRV 40mg	Continuous LDL – calculated mg/dL	9	Mean: 232 SD: 28	8 weeks	9	Mean: 122 SD: 33	Calculated % chance from baseline: -47 P<=0.05	NR
Hunninghake, 2001[3]	Arm 1: (H) ATV 80 mg	Continuous LDL – calculated mg/dL	20	Mean: 182 SE: 3	4 weeks	20	Mean: 86 SE: 5	Change from baseline: -96 SE: 5 P<0.0001 % Change from baseline: -53 SE: 3 P<0.0001	
	Arm 2: (M) Colsevelam 3.8g + ATV 10mg	Continuous LDL -- calculated mg/dL	19	Mean: 187 SE: 4	4 weeks	18	Mean: 98 SE: 5	Change from baseline: -89 SE: 6 P<0.0001 % Change from baseline: -48 SE: 3 P<0.0001	P=0.07
Johansson, 1995[4]	Arm 1: (H) SMV 40 mg	Continuous	26	Mean: 5.74 SD: 0.15	12 weeks	26	NR	Mean change from baseline:	P=0.0001 for 0verall

Author, Year	Arm (Potency)	Outcome Units	Baseline N	Baseline Outcome	Timepoint(s)	N at Timepoint(s)	Outcome at Timepoint(s)	Within Arm Comparisons	Between Arm Comparisons
		LDL -- calculated mmol/l						-2.14 % Change from baseline: -37 P<0.001	between group difference.
	Arm 2: (M) Colestipol 5g +SMV 20mg	Continuous LDL -- calculated mmol/l	29	Mean: 5.64 SD: 0.15	12 weeks	29	NR	Mean change from baseline: -2.01 % Change from baseline: -35 P<0.001	P=0.0001 for 0verall between group difference.
	Arm 3: (M) Colestipol 10g + SMV 20mg	Continuous LDL -- calculated mmol/l	28	Mean: 5.79 SD: 0.17	12 weeks	28	NR	Mean change from baseline: -2.43 % Change from baseline: -42 P<0.001	P=0.0001 for 0verall between group difference.
Knapp, 2001[5]	Arm 1: (M) SMV 20 mg	Continuous LDL – calculated mg/dL	39	Mean: 180 SD: 23	6 weeks	39	Mean: 119 SD: 26	Change from baseline: -61 SD: 21 P<0.0001 % Change from baseline: -34 SD: 11 95%CI: -37, -30 P<0.0001	
	Arm 2: (L) Colsevelam 3.8g + SMV 10mg	Continuous LDL – calculated mg/dL	34	Mean: 196 SD: 49	6 weeks	34	Mean: 116 SD: 43	Change from baseline: -80 SD: 26 P<0.0001 % Change from baseline: -42 SD: 11 95%CI: -46, -38 P<0.0001	P<=0.001
Pravastatin Multicenter Study Group II,	Arm 1: (M) PRV 80 mg	Continuous LDL – calculated	63	Mean: 236 SE: 5.4	8 weeks	61	Mean: 147 SE: 4.3	% Change from baseline: -38 SE: 1.5 P<=0.001	

Author, Year	Arm (Potency)	Outcome Units	Baseline N	Baseline Outcome	Timepoint(s)	N at Timepoint(s)	Outcome at Timepoint(s)	Within Arm Comparisons	Between Arm Comparisons
1993[6]		mg/dL							
	Arm 2: (L) Cholestyramine 24g + PRV 40mg	Continuous LDL – calculated mg/dL	64	Mean: 236 SE: 5.0	8 weeks	63	Mean: 116 SE: 4.6	% Change from baseline: -51% SE: 1.1 P<=0.001	p<=0.001 comparing Arm 1 and Arm 2
Schrott, 1995[7]	Arm 1: (M) LOV 40 mg	Continuous LDL – calculated mg/dL	24	Mean: 195 SE: 3.3	12 weeks	NR	Mean: 120 SE: 3.1	% Change from baseline: -38 P<0.001	
	Arm 2: (L) Colestipol 5g +LOV 20mg	Continuous LDL – calculated mg/dL	23	Mean: 191 SE: 3.3	12 weeks	NR	Mean: 119 SE: 4.8	% Change from baseline: -38 P<0.001	No significant difference between Arm 1 and Arm 2
	Arm 3: (L) Colestipol 10g +LOV 20mg	Continuous LDL – calculated mg/dL	23	Mean: 186 SE: 3.8	12 weeks	NR	Mean: 97 SE: 4.2	% Change from baseline: -48 P<0.001	P<=0.001 comparing Arm 1 vs Arm 3

LDL low density lipoprotein; NR not reported; RSV Rosuvastatin; SD standard deviation

Evidence Table E4. HDL outcome – bile acid sequestrants

Author, Year	**Arm (Potency)**	**Outcome Units**	**Baseline N**	**Baseline Outcome**	**Timepoint(s)**	**N at Timepoint(s)**	**Outcome at Timepoint(s)**	**Within Arm Comparisons**	**Between Arm Comparisons**
2009 Studies									
Barbi, 1992[1] Ismail, 1990[2]	Arm 1: (M) PRV 80 mg	Continuous HDL -- measured mg/dL	9	Mean: 44	8 weeks	9	Mean: 47	Calculated % change from baseline: 1	
	Arm 2: (L) Cholestyramine 24g + PRV 40mg	Continuous HDL -- measured mg/dL	9	Mean: 43	8 weeks	9	Mean: 45	Calculated % change from baseline: 0	NR
Hunninghake, 2001[3]	Arm 1: (H) ATV 80 mg	Continuous HDL -- measured mg/dL	20	Median: 47 IQR: 43, 56	4 weeks	20	Median: 49 IQR: 44, 60	Change from baseline: 2 IQR: -1, 6 P<0.05 % Change from baseline: 5 IQR: -1, 12 P<0.05	
	Arm 2: (M) Colsevelam 3.8g + ATV 10mg	Continuous HDL -- measured mg/dL	19	Median: 46 IQR: 42, 57	4 weeks	18	Median: 51 IQR: 46, 64	Change from baseline: 4 SE: 1, 10 P<0.05 % Change from baseline: 11 IQR: 3, 21 P<0.05	No significant between group differences.
Johansson, 1995[4]	Arm 1: (H) SMV 40 mg	Continuous HDL -- measured	26	Mean: 1.32 SD: 0.06	12 weeks	26	NR	Mean change from baseline: 0.09 % Change from baseline: 8	P=0.008 for 0verall between group difference.

Author, Year	Arm (Potency)	Outcome Units	Baseline N	Baseline Outcome	Timepoint(s)	N at Timepoint(s)	Outcome at Timepoint(s)	Within Arm Comparisons	Between Arm Comparisons
		mmol/l						P<0.001	
	Arm 2: (M) Colestipol 5g +SMV 20mg	Continuous HDL -- measured mmol/l	29	Mean: 1.24 SD: 0.06	12 weeks	29	NR	Mean change from baseline: 0.12 % Change from baseline: 11 P<0.001	P=0.008 for 0verall between group difference.
	Arm 3: (M) Colestipol 10g + SMV 20mg	Continuous HDL -- measured mmol/l	28	Mean: 1.24 SD: 0.07	12 weeks	28	NR	Mean change from baseline: 0.08 % Change from baseline: 7 P<0.05	P=0.008 for 0verall between group difference.
Knapp, 2001[5]	Arm 1: (M) SMV 20 mg	Continuous HDL -- measured mg/dL	39	Median: 48 IQR: 42, 58	6 weeks	39	Median: 52 IQR: 43, 62	Change from baseline: 3 IQR: 0,6 P<0.05 % Change from baseline: 7 IQR: -1, 14 95%CI: 3, 11 P<0.05	
	Arm 2: (L) Colsevelam 3.8g + SMV 10mg	Continuous HDL -- measured mg/dL	34	Median: 49 IQR: 43, 58	6 weeks	34	Median: 53 IQR: 49, 60	Change from baseline: 5 IQR: 2,8 P<0.0001 % Change from baseline: 10 IQR: 3,15 95%CI: 8,14 P<0.0001	NR
Pravastatin Multicenter Study Group II,	Arm 1: (M) PRV 80 mg	Continuous HDL -- measured	63	Mean: 46 SE: 1.2	8 weeks	61	Mean: 46 SEM: 1.5	% Change from baseline: 4.8 SE: 1.4 P<=0.001	

Author, Year	Arm (Potency)	Outcome Units	Baseline N	Baseline Outcome	Timepoint(s)	N at Timepoint(s)	Outcome at Timepoint(s)	Within Arm Comparisons	Between Arm Comparisons
1993[6]		mg/dL							
	Arm 2: (L) Cholestyramine 24g + PRV 40mg	Continuous HDL -- measured mg/dL	64	Mean: 43 SE: 1.5	8 weeks	63	Mean: 46 SEM: 1.5	% Change from baseline: 5.9 SE: 1.4 P<=0.001	NR
Schrott, 1995[7]	Arm 1: (M) LOV 40 mg	Continuous HDL – measured mg/dL	24	Mean: 53 SE: 2.6	12 weeks	NR	Mean: 56 SE: 2.3	% Change from baseline: 6 P<0.01	
	Arm 2: (L) Colestipol 5g +LOV 20mg	Continuous HDL – measured mg/dL	23	Mean: 54 SE: 3.4	12 weeks	NR	Mean: 57 SE: 3.4	% Change from baseline: 6 P<0.01	NR
	Arm 3: (L) Colestipol 10g +LOV 20mg	Continuous HDL – measured mg/dL	23	Mean: 54 SE: 2.8	12 weeks	NR	Mean: 56 SE: 2.6	% Change from baseline: 4 P=0.068	NR

HDL high density lipoprotein; NR not reported; NS non-significant; RSV Rosuvastatin; SD standard deviation

Evidence Table E5. Treatment adherence – bile acid sequestrants

Author, Year	Arm (Potency)	Outcome Units	Timepoint(s)	N at Timepoint(s)	Outcome at Timepoint(s)	Between Arm Comparisons
2009 Studies						
Hunninghake, 2001[3]	Arm 1: (H) ATV 80 mg	Count Pill count	4 weeks	20	88%	
	Arm 2: (M) Colsevelam 3.8g + ATV 10mg	Count Pill count	4 weeks	18	91%	NR
Schrott, 1995[7]	Arm 1: (M) LOV 40 mg	Compliance with drug therapy	12 weeks	NR	97% SE: 1.0	
	Arm 2: (L) Colestipol 5g +LOV 20mg	Compliance with drug therapy	12 weeks	NR	95% SE: 1.7	No significant difference between Arm 1 and Arm 2
	Arm 3: (L) Colestipol 10g +LOV 20mg	Compliance with drug therapy	12 weeks	NR	93% SE: 1.4	No significant difference between Arm 1 and Arm 3

NR not reported; RSV Rosuvastatin

Evidence Table E6. Withdrawal due to adverse events – bile acid sequestrants

Author, Year	Arm (Potency)	Outcome Units	Timepoint(s)	N at Timepoint(s)	Outcome at Timepoint(s)	Between Arm Comparisons
2009 Studies						
Hunninghake, 2001[3]	Arm 1: (H) ATV 80 mg	Count Withdrawal due to adverse events	4 weeks	20	n: 1	
	Arm 2: (M) Colsevelam 3.8g + ATV 10mg	Count Withdrawal due to adverse events	4 weeks	18	n: 1	NR
Knapp, 2001[5]	Arm 1: (M) SMV 20 mg	Count Withdrawal due to adverse events	6 weeks	39	n: 0	
	Arm 2: (L) Colsevelam 3.8g + SMV 10mg	Count Withdrawal due to adverse events	6 weeks	34	n: 1	NR

NR not reported;

Evidence Table E7. Elevated AST or ALT – bile acid sequestrants

Author, Year	Arm (Potency)	Outcome Units	Timepoint(s)	N at Timepoint(s)	Outcome at Timepoint(s)	Between Arm Comparisons
2009 Studies						
Hunninghake, 2001[3]	Arm 1: (H) ATV 80 mg	Count Elevation AST and/or ALT >3x ULN	4 weeks	20	n: 0	
	Arm 2: (M) Colsevelam 3.8g + ATV 10mg	Count Elevation AST and/or ALT >3x ULN	4 weeks	18	n: 0	NR

ALT alanine aminotransferase; AST aspartate aminotransferase; NR not reported; RSV Rosuvastatin.

Evidence Table E8. Study quality assessment – bile acid sequestrants

Author, Year	2009 CER Jadad Score	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14
Barbi, 1992[1] Ismail, 1990[2]	2	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Hunninghake, 2001[3]	4	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Johansson, 1995[4]	2	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Knapp, 2001[5]	5	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Pravastatin Multicenter Study Group II, 1993[6]	3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Schrott, 1995[7]	2	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

CER comparative effectiveness report; H high; L low; N no; NA not applicable; NR not reported; U unclear or unsure.

Q1. What is the risk of selection bias (biased allocation to interventions) due to inadequate generation of a randomized sequence?
Q2. What is the risk of selection bias (biased allocation to interventions) due to inadequate concealment of allocations before assignment?
Q3. For each main outcome or class of outcomes, what is the risk of performance bias due to knowledge of the allocated interventions by participants and personnel during the study (lack of study participant and personnel blinding)?
Q4. Was the care provider blinded to the intervention?
Q5. For each main outcome or class of outcomes, what is the risk of detection bias due to knowledge of the allocated interventions by outcome assessment (lack of outcome assessor blinding)?
Q6. For each main outcome or class of outcomes, what is the risk of attrition bias due to amount, nature, or handling of incomplete outcome data?
Q7. What is the risk of reporting bias due to selective outcome reporting?
Q8. Are there other biases due to problems not covered in 1-6?
Q9. Were all randomized participants analyzed in the group to which they were allocated?
Q10. Were the groups similar at baseline regarding the most important prognostic indicators?
Q11. Were co-interventions avoided or similar?
Q12. Was the compliance acceptable in all groups?
Q13. Was the timing of the outcome assessment similar in all groups?
Q14. Are there other risks of bias?

Evidence Table E9. Study characteristics – ezetimibe

Author, Year Trial #, "Acronym"	Study Design Site(s)	Inclusion Criteria	Participant Statin Use Prior to Trial	Treatment Duration Washout Period Run-In Period	Arms	Subgroup Analyses	Pharmaceutical Industry Support Conflict of Interest disclosures by authors
Ahmed, 2008[8] No	Parallel Arms RCT Single Center Middle East	-Age: 47-62 -Female -Only males -Race/Ethnicity only from the Bahawalpur area -patients without cardiovascular disease -patients without DM -Only patients without thyroid, liver, or chronic kidney disease and without metabolic syndrome- -Patients with LDL-C not at their ATP-III goal level	NR	6-Weeks NA 9-Weeks 3 weeks "washout" and 6 weeks dietary advice	Arm 1: ATV 20mg daily Arm 2: SMV 10mg +Ezetimibe10mg	No subgroup analyses were conducted	Yes, Industry support NR
Araujo, 2010[9] NR	Crossover design Single Center- Central South America	A-ge: 18-75 -Patients with Cardiovascular disease: No uncontrolled heart disease -Not Diabetic, preganant or breast feeding -LDL >160mg/dl - No clinically detectable atherosclerotic disease -No SMV or Ezetimibe hypersensitivity, -No liver transaminases >1.5 times normal or creatinine kinase > 3times normal	NR	4-Weeks Yes NR	Arm 1: SMV 80mg Arm 2: SMV 10mg +Ezetimibe 10mg	No subgroup analyses were conducted	No NR
Averna, 2010[10] No	Parallel Arms RCT Multiple Center Europe	-Age: 18-75 yrs -Patients with Cardiovascular disease: Documented CHD (stable angina with evidence of ischemia on exercise testing, history of MI, percutaneous transluminal coronary angioplasty, atherothrombotic	Prior to trial entry	6-Weeks NA 6-Weeks SMV 20mg daily	Arm 1: SMV 40mg Arm 2: SMV 10mg +Ezetimibe 10mg	No subgroup analyses were conducted	Yes, Industry support Yes, Employee of pharmaceutical company

Author, Year Trial #, "Acronym"	Study Design Site(s)	Inclusion Criteria	Participant Statin Use Prior to Trial	Treatment Duration Washout Period Run-In Period	Arms	Subgroup Analyses	Pharmaceutical Industry Support Conflict of Interest disclosures by authors
		cerebrovascular disease, unstable angina, or non-Q wave myocardial infarction; symptomatic peripheral vascular disease) -Taking a stable daily dose of SMV 20 mg for 6 weeks with good compliance (80% of daily doses for the 6 weeks before baseline visit) and had LDL-C concentration > 100 mg/dL to 160 mg/dL or less - TG< 350 mg/dL, liver transaminases (alanine aminotransferase [ALT] or aspartate aminotransferase [AST]) and creatine phosphokinase (CK) <50% above ULN with no active liver disease, and hematology, blood chemistry, and urinalysis within normal limits -Women of childbearing potential using effective birth control -No class III or IV CHF ; uncontrolled cardiac arrhythmia; recent (within 3 months of randomization) MI, acute coronary insufficiency, coronary artery bypass surgery, or angioplasty; unstable or severe peripheral artery disease; newly diagnosed or unstable angina pectoris; uncontrolled hypertension; uncontrolled endocrine or metabolic disease known to influence serum lipids or lipoproteins; impaired renal function or nephrotic syndrome; or were taking any lipid-lowering agents, fibrates, resins or niacins, or prescription and/or over-the-counter-					

Author, Year Trial #, "Acronym"	Study Design Site(s)	Inclusion Criteria	Participant Statin Use Prior to Trial	Treatment Duration Washout Period Run-In Period	Arms	Subgroup Analyses	Pharmaceutical Industry Support Conflict of Interest disclosures by authors
		drugs with the potential for significant lipid effects or with potential drug interactions with the statins.					
Ballantyne 2003[11]	Parallel Arm RCT Multicenter Unclear	Men and women _18 years of age were screened for primary hypercholesterolemia, defined as calculated LDL-C7 of 145 to 250 mg/dL, inclusive, and triglyceride levels _350 mg/dL. All patients provided written informed consent. Exclusion criteria included congestive heart failure (defined as New York Heart Association class III or IV heart failure8); uncontrolled cardiac arrhythmias; myocardial infarction, coronary bypass surgery, or angioplasty within 6 months of study entry; history of unstable or severe peripheral artery disease within 3 months of study entry; unstable angina pectoris; uncontrolled or newly diagnosed (within 1 month of study entry) diabetes mellitus; unstable endocrine or metabolic diseases known to influence serum lipids and lipoproteins; known impairment of renal function; active or chronic hepatic or hepatobiliary disease; and known coagulopathy.	Lipid therapy was discontinued before trial; 12 weeks for fibrates, 1 year for probucol, and 6 weeks for statins, bile acid sequestrants, nicotinic acid, garlic, fish oil, and other lipid-altering agents	12 weeks 2-12 weeks 2-12 weeks	Arm1: ATV 20mg Arm 2: ATV 40mg Arm 3: ATV 80mg Arm 4: ATV 10mg +Ezetimibe 10mg	None	Funded by pharma, authors employees of pharma.
Ballantyne, 2005[12] NR	Parallel Arm RCT Multicenter	-Men and women, 18 to 79 years, -LDL-C level at or above drug treatment thresholds established by NCEP ATP III, established CHD or CHD risk equivalent with an LDL-C >=130 mg/dL;	All lipid therapy discontinued 7 weeks before trial, fibrates for 9 weeks	6 week NR	Arm1: ATV 10mg Arm 2: ATV 20mg	None	Pharma sponsored study, authors were employees of pharma too.

Author, Year Trial #, "Acronym"	Study Design Site(s)	Inclusion Criteria	Participant Statin Use Prior to Trial	Treatment Duration Washout Period Run-In Period	Arms	Subgroup Analyses	Pharmaceutical Industry Support Conflict of Interest disclosures by authors
	  North America	-No established CHD or CHD risk equivalent, with ≥2risk factors conferring a 10-year risk for CHD >10% and <20% with an LDL-C >=130 mg/dL; no established CHD or CHD risk equivalent, with >=2 risk factors conferring a 10-year risk for CHD <10% with an LDL-C >=160 mg/dL; and no established CHD or CHD risk equivalent, with <2 risk factors, and with LDL-C >=190 mg/dL. -fasting TG level ≤350 mg/dL, ALT and AST, or creatine kinase (CK) level ≤1.5 times ULN, serum creatinine level ≤.5 mg/dL, and HbA1C <9.0% in patients with diabetes.		 4 week placebo run in	Arm 3: ATV 40mg Arm4: ATV 80mg Arm 5: SMV 10mg +Ezetimibe10 Arm 6: SMV 20mg +Ezetimibe 10mg		
Bardini, 2010[13] NCT00423488	Parallel Arms RCT Multiple Center Europe	-Age: 18-75 -Patients with Cardiovascular disease: documented CHD (including stable angina with evi-dence of ischemia on exercise testing, history of MI, percutaneous transluminal coronary angioplasty, atherothrombotic cerebrovascular disease, unstable angina or non-Q wave MI), or symptomatic peripheral vascular disease, who were taking a stable daily dose of SMV 20 mg for 6 weeks with good compliance (80% of daily doses for the 6 weeks prior to baseline visit) and had LDL-C concentration ≥ 2.6 mmol/L (100 mg/dL) to ≤ 4.1 mmol/L (160 mg/dL) were eligible. -Patients were excluded if they had	Prior to trial entry	6 weeks NA NR	Arm 1: SMV 40mg Arm 2: SMV 20mg +Ezetimibe 10mg	No subgroup analyses were conducted	Yes, Industry support Yes, Financial relationship with pharmaceuticals Yes, Employee of pharmaceutical company

Author, Year Trial #, "Acronym"	Study Design Site(s)	Inclusion Criteria	Participant Statin Use Prior to Trial	Treatment Duration Washout Period Run-In Period	Arms	Subgroup Analyses	Pharmaceutical Industry Support Conflict of Interest disclosures by authors
		Class III or IV CHF; uncontrolled cardiac arrhythmia; recent (within 3 months of randomization) myocardial infarction, acute coronary insufficiency, coronary artery bypass surgery, or angioplasty, unstable or severe peripheral artery disease; newly diagnosed or unstable angina pectoris, uncontrolled hypertension (treated or untreated) -DM patients: 18-75 years with T2DM [with fasting plasma glucose ≥ 7.0 mmol/L (126 mg/dL) and HbA1c ≤ 9.0% of at least 12 months duration -TG < 3.99 mmol/L (350 mg/dL), ALT or AST and creatine phosphokinase (CK) < 50% above ULN with no active liver disease, and hematology, blood chemistry, and urinalysis within normal limits. - no uncontrolled endocrine or metabolic disease known to influence serum lipids or lipoproteins; impaired renal function (creatinine > 2.0 mg/dL) or neph-rotic syndrome; or were taking any lipid-lowering agents, fibrates, resins or niacin, or prescription and/or over- the-counter-drugs with the potential for significant lipid effects (other than study drug) or with potential drug interactions with the statins.					
Barrios, 2005[14]	Parallel Arm RCT	-men and women >18 years -documented hypercholesterolaemia	Atorvastatin 10 mg 1 week run-	6 weeks	Arm1: ATV 20mg	-Female , -Race(White,	Yes

Author, Year Trial #, "Acronym"	Study Design Site(s)	Inclusion Criteria	Participant Statin Use Prior to Trial	Treatment Duration Washout Period Run-In Period	Arms	Subgroup Analyses	Pharmaceutical Industry Support Conflict of Interest disclosures by authors
	Multicenter Europe, Asia	and atherosclerotic or CHD. - serum LDL-C between 2.5 and 4.2 mmol/l (100 to 160 mg/dl) and triglycerides (TG) <4.0 mmol/l (350 mg/dl) while on a stable dose of ATV 10 mg for >6 weeks prior to randomization. - Patients of childbearing age were eligible to participate if they had negative pregnancy test results and were considered, by the study investigator, highly unlikely to conceive. - No CHF; MI, coronary artery bypass surgery or angioplasty within the past 3 months; poorly controlled or newly diagnosed (within 3 months) Type I or II diabetes; uncontrolled hypertension (systolic >160 mmHg or diastolic >100 mmHg); uncontrolled endocrine or metabolic disease known to influence serum lipids; ALT and AST levels >1.5 times the ULN) and creatine kinase (CK) levels >1.5 times ULN.	in. Other agents were discontinued	NR 1 week Patients received open-label ATV 10 mg and counseling for a low-cholesterol diet	Arm 2: SMV 20mg +Ezetimibe 10mg	Non-white, -DM	Yes
Bays, 2004	Factorial RCT Multicenter Multinational	- men and women aged 18 to 80 years -primary hypercholesterolemia defined as LDL-C concentrations ≥145 mg/dL but ≤250 mg/dL and TG≤350 mg/dL -ALT and AST concentrations ≤.5 times the upper limit of normal (ULN) with no active liver disease and creatine kinase (CK)	All treatments discontinued >=6 weeks before trial (>=8 weeks for fibrates)	12 week NR 4 week single blind placebo run in	Arm1: SMV 10mg Arm 2: SMV 20mg Arm 3: SMV 40mg Arm 4:	None	pharmaceutical company supported study and authors

Author, Year Trial #, "Acronym"	Study Design Site(s)	Inclusion Criteria	Participant Statin Use Prior to Trial	Treatment Duration Washout Period Run-In Period	Arms	Subgroup Analyses	Pharmaceutical Industry Support Conflict of Interest disclosures by authors
		concentrations <=1.5times ULN at visit 2. Individuals were excluded from participating in the study if they met the following criteria: <50% of ideal body weight according to the 1983 Metropolitan Height and Weight tables (or body weight <100 lb), hypersensitivity to statins, or alcohol consumption >14 drinks per week. Pregnant or lactating females were also excluded. Patients of childbearing age were eligible to participate in the study if they were surgically sterilized or considered highly unlikely to conceive due to use of an acceptable method of birth control (eg, oral contraceptives, intrauterine devices, double-barrier methods, hormone implants). Patients with stable/controlled cardiovascular disease, hypertension, or diabetes mellitus were also allowed to participate in this study			SMV 80mg Arm 5: SMV 10mg +Ezetimibe 10mg Arm 6: SMV 20mg +Ezetimibe 10mg Arm 7: SMV 40mg +Ezetimibe 10mg Arm 8: SMV 80mg +Ezetimibe 10mg Arm 9: Placebo		
Catapano, 2006[15] NCT00090298	Parallel Arm RCT Multicenter NR	-Men and women 18–81 years of age - LDL-C ≥145 mg/dL (3.7 mmol/L) and ≤ 250 mg/dL (6.5 mmol/L) -fasting serum TG level ≤ 350 mg/dL (4.0 mmol/L), - ALT, AST, or creatine kinase (CK) level ≤ 1.5 times the ULN, -serum creatinine level ≤ 1.5 mg/dL (133 mmol/L), -HbA1c < 9.0% in patients with diabetes	Patients discontinued fibrate and all other lipid lowering therapy at 9 and 7 weeks, respectively,	6 weeks Patients discontinued fibrate and all other lipid lowering therapy at 9 and 7 weeks, respectively, before the start of the study	Arm 1: RSV 10mg Arm 2: SMV 20mg +Ezetimibe 10mg Arm 3: RSV 20mg Arm 4: SMV 40mg* +Ezetimibe 10mg	NR	Study funded by pharmaceutical company. Authors have pharmaceutical company COI disclosures.

Author, Year Trial #, "Acronym"	Study Design Site(s)	Inclusion Criteria	Participant Statin Use Prior to Trial	Treatment Duration Washout Period Run-In Period	Arms	Subgroup Analyses	Pharmaceutical Industry Support Conflict of Interest disclosures by authors
				4 weeks placebo/diet run in period	Arm 5: RSV 40mg Arm 6: SMV 80mg* +Ezetimibe 10mg *This arm included only in population characteristics to fully describe study population; however, will not be included in further description or analyses as it is ineligible;		
Cho, 2011[16] NR	Parallel Arms RCT Single Center Asia	-Age: 20-79 -Patients with coronary artery disease and documented hypercholesterolemia (LDL-C >100 mg/dL and ≤250 mg/dL), -presence of established cardiovascular disease plus (1) multiple major risk factors (es pecially DM, (2) poorly controlled risk factors {especially continued cigarette smoking, uncontrolled blood pressure and low high density lipoprotein-cholesterol (HDL-C)}, (3) multiple risk factors of the metabolic syndrome {especially high triglycerides (TG) ≥200 mg/dL plus	Prior statin use	8-Weeks NA 4-Weeks	Arm 1: ATV 20 mg Arm 2: SMV 20mg +Ezetimibe 10 mg	No subgroup analyses were conducted	NR NR

Author, Year Trial #, "Acronym"	Study Design Site(s)	Inclusion Criteria	Participant Statin Use Prior to Trial	Treatment Duration Washout Period Run-In Period	Arms	Subgroup Analyses	Pharmaceutical Industry Support Conflict of Interest disclosures by authors
		non HDL-C ≥130 mg/dL with low HDL-C (180 mmHg or diastolic blo-od pressure >100 mmHg), evidence of uncontrolled endocrine or metabolic disease known to influence serum lipid pro file, and concomitant excluded drug use (i.e. immunosuppressant, corticosteroids, or potent inhibitors of cytochrome P450 3A4)					
Constance, 2007[17] NR	Parallel Arm RCT Multicenter Asia Australia and New Zealand Central and South America Europe Middle East North America	-men and women ≥18 years of age, diagnosed with T2D, with whole blood HbA1c ≤10%, - ALT and/or AST levels ≤1.5 times the upper limit of normal (ULN), and creatine kinase (CK) levels ≤1.5 times ULN. - Patients on ATV 10 mg for >6 weeks prior to study entry and completed a 4-week, open-label ATV 10 mg/day run-in baseline period. - Patients of childbearing age were eligible if they had negative pregnancy test results and were considered by the study investigator to be highly unlikely to conceive. Key exclusion criteria included CHF defined by New York Heart Association class III or IV; myocardial infarction, coronary artery bypass surgery or angioplasty within 3 months; uncontrolled hypertension (systolic >160 mm Hg or diastolic >100 mm Hg); uncontrolled endocrine or metabolic disease known to influence serum	Patients discontinued from all lipid-altering treatments other than ATV 10 mg for at least 6 weeks before the study start (≥8 weeks for fibrates). Eligible patients entered a 4-week baseline period while continuing to receive open label ATV 10 mg and counseling for a low cholesterol diet	8 weeks NR Patients were on ATV 10 mg for >6 weeks prior to study entry and completed a 4-week, open-label ATV 10 mg/day run-in baseline period in addition to counseling for a low cholesterol diet.	Arm1: ATV 20mg Arm 2: SMV 20mg +Ezetimibe 10mg Arm 3: SMV 40mg +Ezetimibe 10mg* *This arm included only in population characteristics to fully describe study population; however, will not be included in further description or analyses as it is ineligible	-All females -Race - Baseline LDL-C≥3.00 mmol/l,	Authors have pharmaceutical company COI disclosures.

Author, Year Trial #, "Acronym"	Study Design Site(s)	Inclusion Criteria	Participant Statin Use Prior to Trial	Treatment Duration Washout Period Run-In Period	Arms	Subgroup Analyses	Pharmaceutical Industry Support Conflict of Interest disclosures by authors
		lipids or lipoproteins; impaired renal function (creatinine >177 mmol/l) or nephrotic syndrome; alcohol consumption >14 drinks per week and treatment with excluded concomitant medications (i.e. immunosuppressants, corticosteroids or potent inhibitors of cytochrome P450 3A4)					
Davidson, 2002[18] NR	Factorial RCT Multicenter North America	-Men and women ages 18 years and older -primary hypercholesterolemia (plasma LDL-C concentration >145 mg/dl to <250 mg/dl, as calculated by the Friedewald equation and TG >350 mg/dl) -No CHF (defined as New York Heart Association class III or IV heart failure) uncontrolled cardiac arrhythmias; history of unstable or severe peripheral artery disease within three months of study entry; unstable angina pectoris; MI, coronary bypass surgery, or angioplasty within six months of study entry;uncontrolled or newly diagnosed (within one month of study entry) diabetes mellitus; -No active or chronic hepatic or hepatobiliary disease; known impairment of renal function; known coagulopathy; and unstable endocrine disease.	Lipid therapy discontinued before study	12 weeks NA 4 weeks (single blind placebo lead in period)	Arm1: SMV 20mg Arm 2: SMV 40mg Arm 3: SMV 80mg Arm 4: SMV 10mg +Ezetimibe10mg Arm 5: SMV 20mg +Ezetimibe 10mg Arm 6: placebo Arm 7: Ezetimibe 10mg Arm 8: SMV 10mg Arm 9:	None	Yes Yes

Author, Year Trial #, "Acronym"	Study Design Site(s)	Inclusion Criteria	Participant Statin Use Prior to Trial	Treatment Duration Washout Period Run-In Period	Arms	Subgroup Analyses	Pharmaceutical Industry Support Conflict of Interest disclosures by authors
					SMV 80mg +Ezetimibe 10mg		
Feldman, 2004[19]	Parallel Arm RCT Multicenter North America	- men and women 18 to 80 years of age with CHD or CHD risk equivalent disease according to NCEP ATP III guidelines and plasma levels of LDL cholesterol ≥130 mg/dl and triglyceride ≤350 mg/dl. - Premenopausal women with negative pregnancy test results and were surgically sterilized or very unlikely to conceive. - Liver transaminase and creatine kinase levels ≤ 50% above the upper limit of normal, -patients who had discontinued all lipid-lowering agents ≥6 weeks before randomization. NCEP ATP III National Cholesterol Education Program Adult Treatment Panel III; *This arm included only in population characteristics to fully describe study population; however, will not be included in further description or analyses as it is ineligible.	patients had to discontinued all lipid-lowering agents ≥6 weeks before randomization.	5-23 weeks ≥6 weeks 4-week placebo diet run-in period	Arm1: SMV 20mg Arm 2: SMV 10mg +Ezetimibe 10mg Arm 3: SMV 20mg* +Ezetimibe 10mg Arm 4: SMV 40mg* +Ezetimibe 10mg	-Age<65,≥65 -Gender -Race -CHD category -Baseline LDL cholesterol category (<160, ≥160)	pharmaceutical company sponsored,
Florentin, 2011[20]	Parallel Arms RCT Single Center	-Diabetic patients;only patients with first diagnosis of diabetes were included, received no anti diabetic drugs during study -Patients with LDL-C levels above	Yes Prior statin use ever	3-Months NA NR	Arm 1: Monotherapy-simva 40 Arm 2:	No subgroup analyses were conducted	Yes, Industry support No

Author, Year Trial #, "Acronym"	Study Design Site(s)	Inclusion Criteria	Participant Statin Use Prior to Trial	Treatment Duration Washout Period Run-In Period	Arms	Subgroup Analyses	Pharmaceutical Industry Support Conflict of Interest disclosures by authors
NCT00932620	Europe	those recommended by the NCEP-ATP III based on each patient's risk factors following a 3-month period of lifestyle changes - No Subjects with TG > 500 mg/dL (5.65 mmol/L), renal disease (serum creatinine levels >1.6 mg/dL; 141 m mol/L), hypothyroidism (thyroid stimulating hormone [TSH] 4 5 IU/mL) and liver disease (alanine amino- transferase [ALT] and/or aspartate aminotransferase [AST] levels 4 3-fold upper limit of normal [ULN] in two consecutive measurements -Any lipid-lowering drugs had to be stopped for at least 6 weeks before study entry. - Patients with hypertension who were on stable medication for at least 3 months and their blood pressure was adequately controlled			Eze/Simva 10/10		
Foody, 2010[21] NCT00535405	Parallel Arms RCT Multiple Center North America	-Patients with Cardiovascular disease: Participants included in this study were at moderately high risk or high risk (with CHD or CHD risk equiva- lents) with or without atherosclerotic vascular disease (AVD; including a history of MI, stable angina, coronary artery procedures, evidence of clinically significant myocardial ischemia, peripheral arterial disease, AAA, or carotid artery disease) with LDL cholesterol levels >=130 mg/dl (3.36 mmol/L), triglyceride levels <=350 mg/dl, liver transaminases (alanine	Prior statin use	12-Weeks NA 3-Weeks Single blind placebo run-in	Arm 1: ATV 20mg Arm 2: ATV 40mg Arm 3: SMV 20mg +Ezetimibe 10mg Arm 4: ATV 10mg Arm 5: SMV 40mg	-All females -All race: African;American, Asian and Hispanic -Patients with DM (type 1 or 2) -Patients with established vascular disease ;peripheral vascular disease,	Yes Government support Yes, Financial relationship with pharmaceuticals Yes, Employee of pharmaceutical company

Author, Year Trial #, "Acronym"	Study Design Site(s)	Inclusion Criteria	Participant Statin Use Prior to Trial	Treatment Duration Washout Period Run-In Period	Arms	Subgroup Analyses	Pharmaceutical Industry Support Conflict of Interest disclosures by authors
		aminotransferase and aspartate aminotransferase) <= 1.5 times the upper limit of normal (ULN) with no active liver disease, and creatine kinase levels <=2 times ULN (3.96 mmol/L) -No patients with prespecified cardiovascular diseases (congestive heart failure; unstable angina pectoris; MI, coronary artery bypass surgery, angioplasty, or uncontrolled peripheral artery disease <= 3 months of placebo run-in; uncontrolled hypertension), intestinal malabsorption or renal disease, uncontrolled endocrine or metabolic diseases, or treatment with prohibited concomitant therapies (i.e., potent P450 3A4 inhibitors; cyclosporine, danazol or fusidic acid; systemic corticosteroids; anti-obesity medication with 3-month stabilization)			+Ezetimibe 10mg	cerebrovascular disease, and/or CAD -Patients with baseline LDL>=190mg/dL	
Gaudiani, 2005[22]	Parallel Arm RCT Multicenter North America	-Age 30–75 years - T2DM(HbA1c<9%), who had been treated with a stable dose of pioglitazone (15–45 mg/day) or rosiglitazone(2–8 mg/day) for at least 3 months. -Men, post-menopausal women or pre-menopausal women highly unlikely to conceive - No MI or cardiovascular surgery within 3 months of study entry -Stable therapy with other antidiabetic medications - patients already treated with a	Eligible patients received open-label SMV 20mg during a 6- week lipid stabilization period	24 weeks NR patients received SMV 20mg for 6 weeks	Arm1: SMV 40mg Arm2: SMV 20mg +Ezetimibe10mg	-Gender(M,F) -Age (<65,≥65) -Race (White,Black, Hispanic) -Baseline LDL(<130,≥130mg/dl) -Baseline TG(<200,≥200mg/dl) -pioglitazone or	pharmaceutical company sponsored, authors were employees of pharmaceutical company

Author, Year Trial #, "Acronym"	Study Design Site(s)	Inclusion Criteria	Participant Statin Use Prior to Trial	Treatment Duration Washout Period Run-In Period	Arms	Subgroup Analyses	Pharmaceutical Industry Support Conflict of Interest disclosures by authors
		statin, that have a plasma LDL-C >2.6mmol/l(100mg/dl) and TG <6.8mmol/l (600mg/dl) prior to initiation of pre-study statin therapy				rosiglitazone TZD (low or high dose)	
Goldberg, 2004[23]	Factorial RCT Multicenter Multinational	Men and women aged 18 years or older with primary hypercholesterolemia, LDL-C 145-250 mg/dl, TG <=350 mg/dl. No congestive heart failure, arrhythmias, severe peripheral artery disease, MI or CABG within 3months, newly diagnosed or uncontrolled DM, renal impairment, uncontrolled hypertension	Lipid therapy was discontinued prior to trial; 6 weeks for stain and 8 weeks for fibrates	12 weeks 2-12 week 4 week- placebo lead-in (single blinded)	Arm1: SMV 20mg Arm 2: SMV 40mg Arm 3: SMV 80mg Arm 4: SMV 10mg +Ezetimibe 10mg Arm 5: SMV 20mg +Ezetimibe10mg Arm 6: SMV 10mg Arm 7: SMV 40mg +Ezetimibe 10mg Arm 8: SMV 80mg +Ezetimibe 10mg	None	Funded by pharma, authors employees of pharma
Goldberg, 2006[24] Tomassini, 2009[25]	Parallel Arm RCT	-patients with type 2 diabetes -aged 18-80 years -hemoglobin A1c levels of 8.5% or less	Lipid therapy discontinued before trial	6 weeks 3-5 weeks	Arm1: ATV 20mg Arm 2: ATV 40mg	All patients were diabetics	Yes

Author, Year Trial #, "Acronym"	Study Design Site(s)	Inclusion Criteria	Participant Statin Use Prior to Trial	Treatment Duration Washout Period Run-In Period	Arms	Subgroup Analyses	Pharmaceutical Industry Support Conflict of Interest disclosures by authors
Guyton, 2008[26] NR VYTAL study	Multicenter North America			washout/run-in (for lipid therapy before trial) 3-5 weeks washout/run in with placebo	Arm 3: SMV20 +Ezetimibe 10mg Arm 4: ATV 10mg Arm 5: ATV 10mg Ezetimibe 40mg		Yes
Hamdan, 2011[27] No	Parallel Arms RCT Single Center Middle East	-Patients with Cardiovascular disease; Acute coronary syndrome (ACS): Typical signs and symptoms of cardiac ischemia and EKG abnormality like T wave tenting or inversion, ST segment elevation or depression (including J point depression in multiple leads) and pathologic Q waves. -No known sensitivity to drugs, renal dysfunction, unexplained elevation of liver function test, infectious or inflammatory process, pt treated with statin or ezetimibe within 6 weeks	No	12-Weeks NA NR	Arm 1: ATV 20 mg plus Placebo for 12 weeks Arm 2: ATV 10mg +Ezetimibe 10 mg for 12 weeks	No subgroup analyses were conducted	NR NR
Her, 2013 [28]	RCT Asia	Men and women aged 20 to 79 years with a LDL-C >130 mg/dL and triglyceride level <400 mg/dL. No pregnant or breastfeeding women, a history of cerebrovascular accident or myocardial infarction within 3 months of enrollment, serum creatinine >2.0 mg/dL, transaminase	no	8 weeks NA 4 week- dietary lead-in	Arm 1: Atorva 20 mg Arm 2: Rosuva 10 mg Arm 3: Atorva/Ezetimibe 5/5 mg	None	None None

Author, Year Trial #, "Acronym"	Study Design Site(s)	Inclusion Criteria	Participant Statin Use Prior to Trial	Treatment Duration Washout Period Run-In Period	Arms	Subgroup Analyses	Pharmaceutical Industry Support Conflict of Interest disclosures by authors
		level >2_ upper limit of normal (ULN)					
Kawagoe, 2011[29] NR	Parallel Arms RCT Single Center Asia	-patients with hypercholestrolemia	NR	10-Weeks NA NR	Arm 1: FLV 60mg Arm 2: FLV 20mg +Ezetimibe10	No subgroup analyses were conducted	NR NR
Kerzner, 2003[30] NR	Factorial RCT Multicenter Multinational	-mean plasma LDL cholesterol ≥145 mg/dl (3.75 mmol/L) to ≤250 mg/dl (6.47mmol/L) and mean TG ≤350 mg/dl [3.99mmol/L] with no single value >400 mg/dl [4.52 mmol/L]). Exclusion criteria included congestive heart failure (defined as New York Heart Association class III or IV heart failure); uncontrolled cardiac arrhythmias; history of unstable or severe peripheral artery disease within 3 months of study entry; unstable angina pectoris; myocardial infarction, coronary bypass surgery, or angioplasty within 6 months of study entry; uncontrolled or newly diagnosed (within 1 month of study entry) diabetes mellitus; active or chronic hepatic or hepatobiliary disease; known impairment of renal function; known coagulopathy; and unstable endocrine or metabolic disease known to influence serum lipids or lipoproteins.	discontinued the use of all lipid-altering drugs prior to trial	12 weeks 2-12 week 4 week- placebo lead-in (single blinded)	Arm1: LOV 20mg Arm 2: LOV 40mg Arm 3: LOV10mg +Ezetimibe10mg Arm 4: Placebo Arm 5: Ezetimibe 10mg Arm 6: LOV 10mg Arm 7: LOV 20mg +Ezetimibe 10mg Arm 8: LOV 40mg +Ezetimibe 10mg	None	Funded by pharma, authors employees of pharma

Author, Year Trial #, "Acronym"	Study Design Site(s)	Inclusion Criteria	Participant Statin Use Prior to Trial	Treatment Duration Washout Period Run-In Period	Arms	Subgroup Analyses	Pharmaceutical Industry Support Conflict of Interest disclosures by authors
Lee, 2011[31] NR	Parallel Arms RCT Single Center Asia	-Age: 20-79 -Patients with Cardiovascular disease: no history of acute CVA or MI within 3 months of trial entry -LDL-C > 130 mg/dL and triglycerides (TG) < 400 mg/dL - No familial hypercholesterolemia, pregnancy or breastfeeding, serum creatinine > 2.0 mg/dL, transaminase level > 2 × upper limit of normal (ULN), thyroid dysfunction, serum creatine kinase (CK) > 2 . 5 × ULN, infection, inflammatory disease, anti-inflammatory drugs, cancer, or a history of adverse reaction to test drugs.	Prior statin use	8-Weeks NA 4 weeks	Arm 1: ATV20 Arm 2: Z5/ Ezetimibe 5mg	No subgroup analyses were conducted	No No
Lee, 2012[32] NR	Parallel Arms RCT Single Center Asia	-Age: 20-79 -LDL-C levels >130 mg/dL and TG levels between 150 and 499 mg/dL -no familial hypercholesterolemia, pregnancy or breastfeeding, a history of acute CVA, myocardial infarction within 3 months of trial entry, serum creatinine >2.0 mg/dL, transaminase level >2 upper limit of normal (ULN), thyroid dysfunction, serum creatine kinase >2.5 ULN, infection, inflammatory diseases, cancer, or a history of adverse reaction to test drugs.	Yes Prior statin use ever	8-Weeks NA 4-Weeks	Arm 1: ATV 20 mg Arm 2: ATV 5mg Ezetimibe 5mg	No subgroup analyses were conducted	No No
Lee, 2013 [33]	RCT Asia	Men or women aged between 20 and 80 years who had been diagnosed with type 2 diabetes	**No**	12 weeks NA	Arm 1: Ezetimibe/Simvastatin 10/20 mg	None	Pharmaceuticsl support None

Author, Year Trial #, "Acronym"	Study Design Site(s)	Inclusion Criteria	Participant Statin Use Prior to Trial	Treatment Duration Washout Period Run-In Period	Arms	Subgroup Analyses	Pharmaceutical Industry Support Conflict of Interest disclosures by authors
		and hypercholesterolemia. No a history of hypersensitivity to ezetimibe or statins, chronic renal failure hepatic dysfunction, congestive heart failure, stroke, myocardial infarction, or coronary revascularization within the preceding 3 months;		4 weeks- life style modification	Arm2: Atorvastatin 20 mg		
Liberopoulos, 2013[34] NR	Parallel Arms RCT Single Center Europe	-Patients with Cardiovascular disease: no known CVD, symptomatic carotid artery disease, peripheral arterial disease, no AAA -LDL-C levels above those recommended by the NCEP ATIII based on each patient risk factors following a 3-month period of lifestyle changes -No hypertension with a change in their medicine in the last 3 months or an uncontrolled blood pressure - No DM, renal or liver disease -No hypertriglyceridemia (TGs>500 mg/dL (5.65 mmol/L))	Prior statin use	12 Weeks NA NR	Arm 1: SMV 40mg Arm 2: SMV 10mg +Ezetimibe 10mg	No subgroup analyses were conducted	No No
Matsue, 2013[35]	RCT Asia	Men and women aged >20 years with clinically evident CAD and LDL-C >70 mg/dl despite use of 10 mg of atorvastatin for >1 month were assessed for eligibility. Major exclusion criteria included any of the following: hypersensitivity to atorvastatin or ezetimibe; active liver disease or hepatic dysfunction, uncontrolled diabetes, coronary revascularization,	no	12 weeks NA None	Arm 1: Ezetimibe/Atorvastta in 10/10 mg Arm2: Atorvastatin 20 mg	None	None None
McKenney, 2007[36]	Parallel Arm RCT	-Men and women aged >= 21 years, - mean of two consecutive	NR	12 weeks (but only 8 week	Arm1: RSV 20 mg	None	Pharma funded study, authors employees of

Author, Year Trial #, "Acronym"	Study Design Site(s)	Inclusion Criteria	Participant Statin Use Prior to Trial	Treatment Duration Washout Period Run-In Period	Arms	Subgroup Analyses	Pharmaceutical Industry Support Conflict of Interest disclosures by authors
NCT00079638 COMPELL	Multicenter North America	determinations of LDL-C, following a minimum 4-week drug washout period if required, had to be: ≥190 mg/dL (4.9 mmol/L) for patients with 0–1 risk factors, ≥160 mg/dL (4.1 mmol/L) for those with 2 or more risk factors, or ≥130 mg/dL (3.4 mmol/L) for patients with established CHD. The two qualifying lipid determinations could not differ by more than 15% from each other. -Mean TG ≤300 mg/dL (3.4 mmol/L). -No known hypersensitivity to the study drugs;major organ system disease; severe hypertension; diabetes;major cardiovascular event within the previous 12 months; severe heart failure; history of myopathy; active gout; or life expectancy <2 years. -No baseline creatine kinase >3 times upper limit, liver transaminases >1.3 times upper limit, creatinine ≥1.5 mg/dL, estimated creatinine clearance <30 mL/min, or uric acid >1.3 times upper limit of normal. -Women of childbearing potential if they used contraception for the study duration.		outcomes are eligible for our review) 4 weeks, before entry into trial None	Arm 2: SMV 20mg +Ezetimibe 10mg		pharma
Moutzouri, 2011[37]	Parallel Arms RCT Single Center	-Primary hypercholesterolemia. -LDL-C levels above those recommended by NCEP-ATP III	NR	12-Weeks NA	Arm 1: Open-label SMV 40 mg for 12 weeks	No subgroup analyses were	NR

Author, Year Trial #, "Acronym"	Study Design Site(s)	Inclusion Criteria	Participant Statin Use Prior to Trial	Treatment Duration Washout Period Run-In Period	Arms	Subgroup Analyses	Pharmaceutical Industry Support Conflict of Interest disclosures by authors
  NR	 Europe	based on each patient risk factors following a 3- month period of lifestyle changes. -Hypertensive patients with stable medication and BP controlled. -Not currently taking lipid-lowering medication (including having stopped within the past 4 weeks). -No CAD ,symptomatic CVD, AAA, DM, TG >500mg/dl, renal diseases, hypothyroidism, liver diseases, neoplasm, clinical evidence of an inflammatory or infection		 12-Weeks	 Arm 2: RSV 10 Arm 3: Open-label SMV 10mg +Ezetimibe 10 mg for 12 weeks	conducted	No
Moutzouri, 2012[38] NR	Parallel arms RCT Single Center Europe	-Patients with cardiovascular disease: - No known coronary artery disease, symptomatic carotid artery disease, peripheral arterial disease, AAA,DM -patients with LDL-cholesterol levels above those recommended by NCEP ATP III based on each patient risk factors, following a 3-month period of lifestyle changes	NR	NA 3 months 3-month dietary intervention in accordance with the NCEP ATP III guidelines. All participants completed 4-day diet records at baseline and at the end of the treatment period. A dietician prescribed a low fat diet for each patient.	Arm 1: SMV 80mg Arm 2: SMV 10mg +Ezetimibe 10mg	No subgroup analyses were conducted	No No
Okada, 2011[39] NR	Parallel Arms RCT Multiple Center	-Age: ≥20; -Female patients, not pregnant or nursing -Patients with Cardiovascular disease: coronary artery disease	Prior statin use	12- NA NA	Arm 1: ATV 20 mg Arm 2: RSV 5 mg	No subgroup analyses were conducted	Yes, NR

Author, Year Trial #, "Acronym"	Study Design Site(s)	Inclusion Criteria	Participant Statin Use Prior to Trial	Treatment Duration Washout Period Run-In Period	Arms	Subgroup Analyses	Pharmaceutical Industry Support Conflict of Interest disclosures by authors
	Asia	whose LDL-C levels were ≥100 mg/d after at least 4 weeks of treatment with atorvastatin 10 mg/day, or rosuvastatin 2.5 mg/day -No TG >500 mg/dl, -No ALT more than twice the upper limit of normal, Secondary dyslipidemia, ACS, PCI, CABG, stroke within 3 months			Arm 3: ATV 10mg +Ezetimibe 10 mg Arm 4: RSV 2.5mg +Ezetimibe 10 mg		
Ostad, 2009[40] ISRCTN34110682 CEZAR study	Parallel Arms RCT Single Center Europe	-Patients with Cardiovascular disease: Coronary artery disease defined as at least one coronary stenosis >50% or general wall irregularities. No ACS. -LDL-C >100mg/dl endothelial dysfunction of brachial artery defined as flow-mediated dilation	Not	8 weeks No NR	Arm 1: ATV 80mg Arm 2: ATV 10mg + Ezetimibe 10mg	No subgroup analyses were conducted	No No
Pesaro, 2012[41] No	RCT Parallel arms Single Center Central South America	-Age: 18-80 yrs -Patients with Cardiovascular disease: angiographically documented CAD, stable angina, and age between 18 and 80 years. no history of myocardial infarction or revascularization within the last 3 months, moderate/severe left ventricular systolic dysfunction, warfarin treatment, -patients had LDL-C > 70 mg/dL despite ongoing treatment with 20 mg/day of simvastatin for more than four weeks - No malignancy, inflammatory	Prior to trial entry	6 weeks NA NR	Arm 1: SMV 80mg Arm 2: SMV 20mg +Ezetimibe 10mg	No subgroup analyses were conducted	No YesFinancial relationship with pharmaceuticals

Author, Year Trial #, "Acronym"	Study Design Site(s)	Inclusion Criteria	Participant Statin Use Prior to Trial	Treatment Duration Washout Period Run-In Period	Arms	Subgroup Analyses	Pharmaceutical Industry Support Conflict of Interest disclosures by authors
		diseases, severe renal insufficiency (creatinine > 1.5 mg/dL), active liver disease or known liver cirrhosis and unclarified transaminase increase (> 3 fold of normal)					
Piorkowski, 2007[42] NR	Parallel Arm RCT Single center Europe	-age between 18 and 80 years -angiographically documented CAD, -LDL>2.5mmol/l -concurrent medication with aspirin and clopidogrel, and maintained throughout the entire study period. -No myocardial infarction or creatine kinase elevation within the last 4 weeks, recent warfarin treatment, tumors, severe renal insufficiency, active liver disease or known liver cirrhosis,unclarified transaminase increase, recent antibiotic therapy, and known alcohol abuse	ATV 10 mg or 20mg/day	4 weeks None None	Arm1: ATV 40mg Arm 2:ATV 10mg +EZE 10mg	None	NR
Robinson, 2009[43] NCT00409773 VYMET Study	Parallel Arms RCT Multiple Center North America Europe	-Age: 18 to 79 years old -Patients with Cardiovascular disease: Moderately high or high risk of CHD -Diagnosed metabolic syndrome and hypercholesterolemia - Patients with preexisting AVD had to have baseline LDL>=70 mg/dL, all other patients had to have a baseline LDL>=100mg/dL - Naive to lipid-lowering medications or Discontinued medications at least 6 weeks before trial	Yes Prior statin use ever	6-Weeks NA NR	Arm 1: ATV 10mg Arm 2: SMV 20mg +Ezetimibe 10mg Arm 3: ATV 20mg Arm 4: SMV 40mg +Ezetimibe 10mg Arm 5: ATV 40mg	No subgroup analyses were conducted	Yes, Industry support Yes, Financial relationship with pharmaceuticals Yes, Employee of pharmaceutical company
Roeters van Lennep, H.W.O,	Parallel Arm RCT	-men and women > 18 years of age with controlled stable	Patients were required to be	12 weeks (+2 weeks for AE	Arm1: SMV 40 (with SMV	None	Yes

Author, Year Trial #, "Acronym"	Study Design Site(s)	Inclusion Criteria	Participant Statin Use Prior to Trial	Treatment Duration Washout Period Run-In Period	Arms	Subgroup Analyses	Pharmaceutical Industry Support Conflict of Interest disclosures by authors
2007[44] NCT00166530	Multicenter Europe	DM2 (> 3 months) and/or established CHD. -Patients on a stable daily statin dose of either ATV 10 mg or SMV 20 mg for at least 4 weeks. -Entry lipid values while on statin monotherapy were: LDL‑C ≥ 2.5 mmol/L and < 5.0 mmol/L, TG ≤ 4.0 mmol/L and TC ≤ 7.0 mmol/L. - -Female patients who were postmenopausal, surgically sterilized or otherwise judged by the investigator as 'highly unlikely to conceive' during the study due to use of an acceptable method of birth control. - No cholesterol-lowering medication regime changed in the previous 4 weeks, any other investigational drug within 3 months, pregnant or lactating.	on a stable daily statin dose of either ATV 10 mg or SMV 20 mg for at least 4 weeks	monitoring only) NR 4 weeks	20mg during run in) Arm 2: ATV 20mg (with ATV 10mg during run in) Arm 3: SMV 20 +Ezetimibe 10mg (with SMV 20mg during run in) Arm 4: SMV 20mg +Ezetimibe10mg (with ATV 10mg during run in)		Authors were employed by pharmaceutical industry
Rudofsky, 2012[45] NR	Parallel Arms RCT Single Center Europe	-Age: 35-80 yrs old -type 2 DM with HbA1c between 6 and 9%. -Patients with elevated LDL-c values > 100 mg/dl with no lipid-lowering treatment within the last six month - No uncontrolled hypertension and/or aspirin or corticoids in their medication*	NR	8-Weeks NA NR	Arm 1: SMV 80mg Arm 2: SMV 10mg +Ezetimibe 10mg Arm 3: Placebo	No subgroup analyses were conducted	Study funded by pharmaceutical companies. No
Stein, 2004[46]	Parallel Arm RCT Multicenter North America,	Eligible patients were _18 years old, with primary hypercholesterolemia and documented CHD, at least 2 cardiovascular risk factors, or HeFH with a LDL-C level _130 mg/dL despite	a6- to 14-week non-blinded phase, during which 10 mg/day of ATV was	9 weeks** None 6-14 weeks*	Arm1: ATV 20 mg Arm 2: ATV 10 mg +Ezetimibe 10mg	None	Yes

Author, Year Trial #, "Acronym"	Study Design Site(s)	Inclusion Criteria	Participant Statin Use Prior to Trial	Treatment Duration Washout Period Run-In Period	Arms	Subgroup Analyses	Pharmaceutical Industry Support Conflict of Interest disclosures by authors
	Europe (21 countries- not specified)	treatment with 10 mg/day of atorvastatin and diet (NCEP step 1 or stricter). No serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) determinations _2-times the upper limit of normal (ULN); significant renal or endocrine disease; pregnancy or lactation; advanced congestive heart failure (New York Heart Association class III or IV); uncontrolled cardiac arrhythmias; unstable angina pectoris, myocardial infarction, or surgical or percutaneous coronary revascularization within 3 months of study entry; or ongoing treatment with lipid-lowering agents other than 10 mg/day of atorvastatin.	initiated, other lipid-lowering medications were discontinued	*a 6- to 14-week nonblinded phase, during which 10 mg/day of atorvastatin was initiated, other lipid-lowering medications were discontinued, and a NCEP step 1 or stricter diet was stabilized ** I have included outcomes for 4 weeks only, doses were doubled after 4 weeks			
Yamazaki, 2013[47] UMIN000003746	Parallel Arms RCT Multiple Center Asia	-Patients with Cardiovascular disease: undergone percutaneous coronary intervention for CAD -LDL-C levels >70 mg/dl (above secondary prevention target for high-risk CAD), -hs-CRP levels> 1.0 mg/dl	NR	12 Weeks NA NR	Arm 1: RSV 10 mg Arm 2: RSV 2.5mg +Ezetimibe 10 mg	No subgroup analyses were conducted	NR No
Zieve, 2010[48] Ben-Yehida, 2011[49] NCT00418834	Parallel Arms RCT Multiple Center North America Europe	-Age: >=65 years old -Patients with Cardiovascular disease: Established coronary heart disease and other AVD and LDL cholesterol >=70 but <=160 mg/dl; no AVD but diabetes mellitus (type 1 or 2) or multiple risk factors and a 10-year risk of coronary heart	Prior to trial entry	6-Weeks NA 4-Weeks ATV 10 mg daily	Arm 1: ATV 20mg Arm 3: ATV 10mg + Ezetimibe 10mg	-All elderly patients older than 80 -All females -Patients with DM (type 1 or 2) -Patients with	Yes, Industry support Yes, Financial relationship with pharmaceuticals Yes, Employee of pharmaceutical

Author, Year Trial #, “Acronym”	Study Design Site(s)	Inclusion Criteria	Participant Statin Use Prior to Trial	Treatment Duration Washout Period Run-In Period	Arms	Subgroup Analyses	Pharmaceutical Industry Support Conflict of Interest disclosures by authors
ZETia in the ELDerly [ZETELD] Study		disease of >20% (as determined by the Framingham calculation) and LDL cholesterol >=100 but <=190 mg/dl -TG<=350 mg/dl, alanine aminotransferase and aspartate aminotransferase <=1.5 times the ULN with no active liver disease, creatine kinase <=2 times the upper limit of normal, TSH >=0.3 or <=5.0 IU/ ml,				established vascular disease(peripheral vascular disease, cerebrovascular disease, and/or CAD)	company

AAA abdominal aortic aneurysm; ACS acute coronary syndrome; AE adverse event; ALT alanine aminotransferase; AST aspartate aminotransferase; ATV atorvastatin; CABG coronary artery bypass graft; CAD coronary artery disease; CHF congestive heart failure; CVA cerebrovascular accident; CVD cardiovascular disease; DM diabetes mellitus; FLV fluvastatin; NCEP ATPIII national cholesterol education program adult treatment panel III ;T2D Type 2 diabetes mellitus; HbA1c hemoglobin A1c; hs –CRP high sensitivity C-reactive protein; LDL low density lipoprotein; MI myocardial infarction; PCI percutaneous coronary intervention; RCT randomized control trial; RSV rosuvastatin; ULN upper limit of normal; SMV simvastatin; TG triglyceride TSH thyroid stimulating hormone

* conditions known to modulate mononuclear NF-kB activation

Evidence Table E10. Baseline characteristics – ezetimibe

Author, Year	Arms	N	Age	Female N (%)	Race N (%)	Smoking Status N (%)	Prior Stroke N (%)	Prior MI N (%)	Prior REVASC N (%)	DM N (%)	LDL	Between Group Differences
Ahmed, 2008[8]	Arm 1: ATV 20mg Arm 2: SMV 10mg +Ezetimibe 10mg	Arm 1: 111 (50.7) Arm 2: 108 (49.3)	Arm 1: Mean: 54, SD: +/-7 Arm 2: Mean: 55, SD: +/-7	Arm 1: N: 0 (0) Arm 2: N: 0 (0)	NR	NR	NR	Arm 1: 0(0) Arm 2: 0(0)	Arm 1: 0(0) Arm 2: 0(0)	Arm 1: 0(0) Arm 2: 0(0)	Arm 1: Mean: 179, SD: +/-38 Arm 2: Mean: 180, SD: +/-35	NR
Araujo, 2010[9]	Arm 1: SMV 80mg Arm 2: SMV10mg +Ezetimibe 10mg	Arm 1: 12(cross over) Arm 2: 11(cross over)	NR	NR	NR	NR	NR	NR	NR	NR	Arm 1: Mean: 205.78, SD: 41.96 Arm 2: Mean: 200.66, SD: 42.83	NR
Averna, 2010[10]	Arm 1: SMV 40mg Arm 2: SMV 10mg +Ezetimibe10 mg	Arm 1: 56 Arm 2: 56	Arm 1: Mean: 62, SD: 7.8 Arm 2: Mean: 61, SD: 8.4	Arm 1: 24(42.9) Arm 2: 26 (46.4)	NR	NR	Arm 1: 20 (35.7) Arm 2: 22(39.3)	Arm 1: 15 (26.8) Arm 2: 13(23.2)	NR	NR	Arm 1: Mean:128, SD: 16.6 Arm 2: Mean: 125.9, SD: 16.3	NR
Ballantyne 2003[11]	Arm1: ATV 20mg Arm 2: ATV 40mg Arm 3: ATV 80mg Arm 4: ATV 10mg +Ezetimibe10	*All ATV arms: 248 *All Ezetimibe/ATV arms: 255	All ATV arms: Mean:57.8 SD: 11.7 All Ezetimibe/ ATV arms: Mean:	All ATV arms: 153 (62%) All Ezetimibe/ ATV arms 148(58%)	All ATV arms: White: 205(83%) All Ezetimibe/ ATV arms White: 222(87%)	All ATV arms: Current smoker: 33 (13%) All Ezetimibe/ ATV arms Current smoker: 35 (14%)	All ATV arms: 23 (9%) All Ezetimibe/ ATV arms: 23 (9%)	NR	All ATV arms: 7 (3%) All Ezetimibe/ ATV arms: 8(3%)	All ATV arms: 11(4%) All Ezetimibe/ ATV arms: 17 (7%)	All ATV arms: Mean:4.65 SE: 0.04 All Ezetimibe/ ATV arms: Arm 2: Mean:4.65 SE: 0.04	none

Author, Year	Arms	N	Age	Female N (%)	Race N (%)	Smoking Status N (%)	Prior Stroke N (%)	Prior MI N (%)	Prior REVASC N (%)	DM N (%)	LDL	Between Group Differences
	mg		58.7 SD: 11.4								LDL is in mmol/l	
Ballantyne, 2005[12]	Arm1: ATV 10mg Arm 2: ATV 20mg Arm 3: ATV 40mg Arm4: ATV 80mg Arm 5: SMV 10mg +Ezetimibe 10mg Arm 6: SMV 20mg + Ezetimibe 10mg	All ATV arms: 951 All Ezetimibe/SMVarms: 951*	All ATV arms: Mean: 58.5 SD: 10.2 All Ezetimibe/ SMV arms Mean: 59.0 SD: 10.6	All ATV arms: 453(47.6%) All Ezetimibe/ SMV arms: 455 (48%)	All ATV arms: White: 818(86.0%) Black: 71(7.5%) Hispanic: 45(4.7%) All Ezetimibe/ SMV arms White: 821(86.3%) Black: 72(7.6%) Hispanic: 42 (4.4%)	NR	NR	NR	NR	NR	NR	None
Bardini, 2010[13]	Arm 1: SMV 40mg Arm 2: SMV 20mg +Ezetimibe 10mg	Arm 1: 50 Arm 2: 37	Arm 1: Mean: 64, SD: 6.1 Arm 2: Mean: 65, SD: 6.5	Arm 1: 12 (24) Arm 2: 16 (43.2)	Arm 1: White: (100) Arm 2: White: (100)	NR	Arm 1: 27 (54) Arm 2: 22 (59.5)	Arm 1: 5 (10) Arm 2: 3 (8.1)	NR	Arm 1: 50 (100) Arm 2: 37 (100)	Arm 1: Mean: 3.2, SD: 0.5 Arm 2: Mean: 3.3, SD: 0.5	NR
Barrios, 2005[14]	Arm1: ATV 20mg Arm 2:	Arm 1: 214 Arm 2:	Arm 1: Mean:63.4 SD: 10.2	Arm 1: 86(40.2%) Arm 2:	Arm 1: White: 197(92.1%) Black: 3(1.4%)	NR	NR	NR	NR	Arm 1: 53 (24.8%) Arm 2:	Arm 1: Mean: 3.24 SD: 0.49 Arm 2: Mean: 3.19	None

Author, Year	Arms	N	Age	Female N (%)	Race N (%)	Smoking Status N (%)	Prior Stroke N (%)	Prior MI N (%)	Prior REVASC N (%)	DM N (%)	LDL	Between Group Differences
	SMV 20mg +Ezetimibe 10mg	221	Arm 2: Mean:63.5 SD:9.6	80(36.2%)	Arm 2: White: 205(92.8%) Black: 1(0.5%)					59(26.7%)	SD: 0.45 *LDL in mmol/L	
Bays, 2004[50]	Arm1: SMV 10mg Arm 2: SMV 20mg Arm 3: SMV 40mg Arm 4: SMV 80mg Arm 5: SMV 10mg +Ezetimibe 10mg Arm 6: SMV 20mg +Ezetimibe 10mg Arm 7: SMV 40mg +Ezetimibe 10mg Arm 8: SMV 80mg +Ezetimibe 10mg Arm 9: Placebo	Placebo: 148 Ezetimibe: 149 Pooled SMV: 622 Pooled Ezetimibe/SMV: 609	Placebo: Mean: 56.0 SD:10.8 Ezetimibe: Mean: 55.5 SD:11.0 Pooled SMV: Mean: 54.9 SD:11.2 Pooled Ezetimibe/ SMV: Mean:56.4 SD:10.6	Placebo: 83 (56.1%) Ezetimibe: 81 (54.4%) Pooled SMV: 315 (50.6%) Pooled Ezetimibe/ SMV: 313 (51.4%)	Placebo: White: 132(89.2%) Black: 5(3.4%) Hispanic: 2 (1.4%) Ezetimibe: White: 133(89.3%) Black: 4(2.7%) Hispanic: 4(2.7%) Pooled SMV: White: 541(87%) Black: 21 (3.4%) Hispanic: 43(6.9%) Pooled Ezetimibe/ SMV: White: 540(88.7%) Black: 19(3.1%) Hispanic: 8 (1.3%)	NR	NR	NR	NR	NR	Placebo: Mean: 177.9 SD: 22.8 Ezetimibe: Mean: 179.9 SD: 23.1 Pooled SMV: Mean: 177.5 SD: 25.3 Pooled Ezetimibe/ SMV: Mean: 176.2 SD: 24.8	NR

Author, Year	Arms	N	Age	Female N (%)	Race N (%)	Smoking Status N (%)	Prior Stroke N (%)	Prior MI N (%)	Prior REVASC N (%)	DM N (%)	LDL	Between Group Differences
Catapano, 2006[15]	Arm 1: RSV 10mg* Arm 2: RSV 20mg Arm 3: RSV 40mg Arm 4: SMV 20mg +Ezetimibe 10mg Arm 5: SMV 40mg* +Ezetimibe10 mg Arm 6: SMV 80* +Ezetimibe10 mg	Arm 1:492 Arm 2: 495 Arm 3: 494 Arm 4: 492 Arm 5: 493 Arm 6: 493	Arm 1: Mean:55.6 SD:10.3 Arm 2: Mean:55.8 SD:10.4 Arm 3: Mean:55.4 SD:10.6 Arm 4: Mean:54.9 SD:10.4 Arm 5: Mean:56.2 SD:10.4 Arm 6: Mean:55.9 SD:10.0	Arm 1: 286(58.1) Arm 2: 280(56.6) Arm 3: 291(58.9 Arm 4: 255(51.8) Arm 5: 272(55.2) Arm 6: 273(53.4)	Arm 1: White: 427(86.8) Black: 31(6.3) Hispanic: 25(5.1) Arm 2: White: 421(85.1) Black: 35(7.1) Hispanic: 24 (4.8) Arm 3: White: 425 (86.0) Black: 38(7.7) Hispanic: 19(3.8) Arm 4: White: 431 (87.6) Black: 30(6.1) Hispanic: 20 (4.1) Arm 5: White: 429 (87.0) Black: 30(6.1) Hispanic:	NR	NR	NR	NR	NR	Arm 1: Mean:172 SD:NR Arm 2: Mean:173 SD:NR Arm 3: Mean:173 SD:NR Arm 4: Mean:172 SD:NR Arm 5: Mean:173 SD:NR Arm 6: Mean:172 SD:NR	Significant between group differences

Author, Year	Arms	N	Age	Female N (%)	Race N (%)	Smoking Status N (%)	Prior Stroke N (%)	Prior MI N (%)	Prior REVASC N (%)	DM N (%)	LDL	Between Group Differences
					19(3.9) Arm 6: White: 426 (86.4) Black: 37(7.5) Hispanic: 16 (3.2)							
Cho, 2011[16]	Arm 1: ATV 20 mg Arm 2: SMV 20mg +Ezetimibe 10 mg)	Arm 1: 43 (50.6) Arm 2: 42 (49.4)	Arm 1: Mean: 62.6, SD: 9.7 Arm 2: Mean: 60.5, SD: 9.5	Arm 1: NR (42.1) Arm 2: NR (33.1)	NR	Arm 1: Current: NR (42.1), Former: NR, Current/Former: NR, Never: NR Arm 2: Current: NR (27.8), Former: NR, Current/Former: NR, Never: NR	NR	NR	NR	Arm 1: N: NR (57.9) Arm 2: N: NR (66.7)	Arm 1: Mean: 32.1, SD: 30.6 Arm 2: Mean: 134.1, SD: 23.2	NR
Constance, 2007[17]	Arm1: ATV 20mg Arm 2: SMV 20mg +Ezetimibe 10mg Arm 3: SMV 40mg +Ezetimibe 10mg*	Arm 1: 219 Arm 2: 220 Arm 3: 222	Arm 1: Mean:61.7 Range: 29-83 Arm 2: Mean: 62.1 Range: 28-86 Arm 3: Mean:62.4 SD:35-84	Arm 1: 111(50.7) Arm 2: 108(49.1) Arm 3: 110(49.5)	Overall White(73.7) Arm 1: White:NR Black:NR Hispanic: NR Arm 2: White: NR Black:NR Hispanic: NR Arm 3: White: NR Black: NR Hispanic: NR	NR	NR	NR	NR	Arm 1: 219(100) Arm 2: 220(100) Arm 3: 222(100)	Arm 1: Mean: 2.42 SD: 0.69 Arm 2: Mean: 2.35 SD: 0.69 Arm 3: Mean: 2.48 SD: 0.69	no clinically meaningful differences in baseline demographic, anthropometric or disease characteristics across treatment groups *This arm included only in population characteristics to fully

Author, Year	Arms	N	Age	Female N (%)	Race N (%)	Smoking Status N (%)	Prior Stroke N (%)	Prior MI N (%)	Prior REVASC N (%)	DM N (%)	LDL	Between Group Differences
												describe study population; however, will not be included in further description or analyses as it is ineligible
Davidson, 2002[18]	Arm1: SMV 20mg Arm 2: SMV 40mg Arm 3: SMV 80mg Arm 4: SMV 10mg +Ezetimibe10 mg Arm 5: SMV 20mg +Ezetimibe 10mg Arm 6: placebo Arm 7: Ezetimibe 10mg Arm 8: SMV 10mg Arm 9: SMV 80mg	*Placebo: 70 *Ezetimibe: 61 *All SMV: 263 *All Ezetimibe/SMV: 274	*Placebo: Mean:58.8 Range: 25-84 *Ezetimibe: Mean: 60.3 Range: 35-84 *All SMV: Mean: 56.4 Range: 25-87 *All Ezetimibe/ SMV: Mean: 57.6 Range: 27-83	*Placebo: 39 (56%) *Ezetimibe: 37 (61%) *All SMV: 153 (58%) *All Ezetimibe/ SMV: 148 (54%)	*Placebo: White:67 (96%) Black:1(1%) Hispanic:1 (1%) *Ezetimibe: White: 58 (95%) Black: 1(2%) Hispanic: 2(3%) *All SMV White: 237 (90%) Black: 12(5%) Hispanic: 13(5%) *All Ezetimibe/ SMV: White: 248(91%) Black: 11(4%) Hispanic:	*Placebo: 8 (11%) *Ezetimibe: 9 (15%) *All SMV: 41 (16%) *All Ezetimibe/ SMV : 37 (14%)	*Placebo: 5 (7%) *Ezetimibe: 3 (5%) *All SMV: 16 (6%) *All Ezetimibe/ SMV: 23 (8%)	NR	NR	NR	*Placebo: Mean: 177.4 SD: 21.7 *Ezetimibe: Mean: 181.3 SD: 23.0 *All SMV: Mean: 178.5 SD: 20.0 *All Ezetimibe/ SMV Mean: 176.3 SD: 19.9	None significant

Author, Year	Arms	N	Age	Female N (%)	Race N (%)	Smoking Status N (%)	Prior Stroke N (%)	Prior MI N (%)	Prior REVASC N (%)	DM N (%)	LDL	Between Group Differences
	+Ezetimibe 10mg				9 (3%)							
Feldman, 2004[19]	Arm1: SMV 20mg Arm 2: SMV 10mg +Ezetimibe10 mg Arm 3: SMV 20mg +Ezetimibe 10mg* Arm 4: SMV 40mg +Ezetimibe 10mg*	Arm 1: 253 Arm 2: 251 Arm 3: 109 Arm 4: 97	Arm 1: Mean:62.1 SD:9.7 Arm 2: Mean:61.3 SD:10.2 Arm 3: Mean: 64.0 SD:9.8 Arm 4: Mean:61.7 SD:9.8	Arm 1:95 (38) Arm 2: 78(31) Arm3: 50(46) Arm 4: 37(38)	Arm 1: White: 208(82) Black:18(7) Hispanic: NR Arm 2: White: 207(82) Black: 22(9) Hispanic: NR Arm 3: White: 90(83) Black: 11(10) Hispanic: NR Arm 4: White: 82(84) Black: 7(7) Hispanic: NR	NR	Arm 1: 140(55) Arm 2: 123(49) Arm 3: 49(45) Arm 4: 56(58)	NR	NR	Arm 1: 86(34) Arm 2: 95(38) Arm 3: 38(35) Arm 4: 23(24)	Arm 1: Mean: 173.8 SD:44.7 mg/dl Arm 2: Mean: 165.1 SD:34.3 Arm 3: Mean: 167.3 SD:33.0 Arm 4: Mean:170.5 SD:40.6	NR
Florentin, 2011[20]	Arm 1: SMV 40mg Arm 2: SMV10mg +Ezetimibe 10mg	Arm 1: 50 Arm 2: 50	Arm 1: Mean: 57, SD: 10 Arm 2: Mean: 59, SD: 9	Arm 1: 16(32) Arm 2: 17(34)	NR	Arm 1: Current: 11 (22), Current/Never %: NR Arm 2: Current: 7 (14), Current/Never %: NR	NR	NR	NR	Arm 1: 3(6) Arm 2: 5(10)	Arm 1: Mean: 172, SD: 31 Arm 2: Mean: 178, SD: 31	NR
Foody, 2010[21]	Arm 1: ATV 20 mg	Arm 1: 259	Arm 1: Mean: 71.7,	Arm 1: 175 (68)	Arm 1: White: 209 (81), Black: 8	NR	NR	NR	NR	Arm 1: 41(16)	Arm 1: Mean: 165, SD: 29	NR

Author, Year	Arms	N	Age	Female N (%)	Race N (%)	Smoking Status N (%)	Prior Stroke N (%)	Prior MI N (%)	Prior REVASC N (%)	DM N (%)	LDL	Between Group Differences
	Arm 2: ATV 40mg Arm 3: SMV20mg +Ezetimibe10 Arm 4: ATV10 mg Arm 5: SMV40mg +Ezetimibe10 mg	Arm 2: 257 Arm 3: 259 Arm 4: 257 Arm 5: 257	SD: 5.2 Arm 2: Mean: 72.1, SD: 5.1 Arm 3: Mean: 71.8, SD: 5.5 Arm 4: Mean: 72.1, SD: 5.7 Arm 5: Mean: 72.2, SD: 5.6	Arm 2: 163 (63) Arm 3: 146 (56) Arm 4: 172 (67) Arm 5: 153 (60)	(3), Asian: 12 (5), Specific: 30 (12) Arm 2: White: 210 (82), Black: 9 (4), Asian: 10 (4), Specific: 28 (11) Arm 3: White: 224 (87), Black: 2 (1), Asian: 6 (2), Specific: 27 (10) Arm 4: White: 224 (87), Black: 2 (1), Asian: 10 (4), Specific: 21 (8) Arm 5: White: 214 (83), Black: 6 (2), Asian: 8 (3), Specific: 29 (11)					Arm 2: 31(12) Arm 3: 39(15) Arm 4: 25(10) Arm 5: 38 (15)	Arm 2: Mean: 168, SD: 30 Arm 3: Mean: 166, SD: 30 Arm 4: Mean: 167, SD: 34 Arm 5: Mean: 163, SD: 29	

Author, Year	Arms	N	Age	Female N (%)	Race N (%)	Smoking Status N (%)	Prior Stroke N (%)	Prior MI N (%)	Prior REVASC N (%)	DM N (%)	LDL	Between Group Differences
Gaudiani, 2005[22]	Arm1: SMV 40mg Arm2: SMV 20mg +Ezetimibe10 mg	Arm1: 110 Arm2: 104	Arm 1: Mean: 58.3 Range: 37-78 Arm 2: Mean: 57.8 Range: 35-80	Arm 1: 49(44.5) Arm 2: 42(40.4)	Arm 1: White: 61 (55.5) Black: 13(11.8) Hispanic: 25(24.0) Arm 2: White: 55 (52.9) Black: 16(15.4) Hispanic: 25 (24.0)	NR	NR	NR	NR	Arm 1: 110 (100) Arm2: 104(100)	Arm 1: Mean: 2.37 SD: 0.63 mmol/l Arm 2: Mean: 2.43 SD: 0.74 mmol/l	NR
Goldberg, 2004[23]	Arm1: SMV 20mg Arm 2: SMV 40mg Arm 3: SMV 80mg Arm 4: SMV 10mg +Ezetimibe10 mg Arm 5: SMV 20mg Ezetimibe 10mg Arm 6: SMV 10mg Arm 7: SMV 40mg +Ezetimibe 10mg	*Placebo: 93 *Ezetimibe: 92 *All SMV: 349 *All Ezetimibe/SMV: 353	NR	*Placebo: 55(59%) *Ezetimibe: 57 (62%) *All SMV: 177 (51%) *All Ezetimibe/ SMV: 184 (52%)	*Placebo: White: 75 (81%) Black: 5(5%) Hispanic: 8 (9%) *Ezetimibe: White: 71 (77%) Black: 6(7%) Hispanic: 9(10%) *All SMV White: 277 (79%) Black: 14(4%) Hispanic: 35(10%) *All Ezetimibe/	NR	NR	NR	NR	NR	NR	NR

Author, Year	Arms	N	Age	Female N (%)	Race N (%)	Smoking Status N (%)	Prior Stroke N (%)	Prior MI N (%)	Prior REVASC N (%)	DM N (%)	LDL	Between Group Differences
	Arm 8: SMV 80mg +Ezetimibe 10mg				SMV: White: 294(83%) Black: 10(3%) Hispanic: 31(9%)							
Goldberg, 2006[24] Guyton, 2008[26] Tommassini, 2009[25]	Arm1: ATV 20mg Arm 2: ATV 40mg Arm 3: SMV 20mg +Ezetimibe 10mg *Arm4: ATV 10mg *Arm5: SMV 40 +Ezetimibe 10mg	Arm 1: 245 Arm 2: 245 Arm 3: 247 Arm 4: 245 Arm 5: 247	Arm 1: Mean: 60.1 SD: 10.6 Arm 2: Mean: 59.9 SD: 10.4 Arm 3: Mean: 59.8 SD: 10.3 Arm 4: Mean: 59.1 SD: 10.1 Arm 5: Mean: 58.7 SD: 10.2	Arm 1: 125(51%) Arm 2: 114 (46.5%) Arm 3: 125 (50.6%) Arm 4: 135 (55.1%) Arm 5: 148(59.9 %)	Arm 1: White: 182(74.3%) Black: 28(11.4%) Hispanic: 22 (9%) Asian: 9 (3.7%) Arm 2: White: 192(78.4%) Black: 22(9%) Hispanic: 24 (9.8%) Asian: 6 (2.4%) Arm 3: White: 180(72.9%) Black: 30(12.1%) Hispanic: 23(9.3%) Asian: 6 (2.4%) Arm 4: White: 180(73.5%) Black:	NR	NR	NR	NR	Arm 1: 245(100 %) Arm 2: 245(100 %) Arm 3: 247(100 %) Arm 4: 245(100 %) Arm 5: 247(100 %)	Arm 1: Mean: 146.6 Arm 2: Mean: 145.9 Arm 3: Mean: 145.0 Arm 4: Mean: 145.2 Arm 5: Mean: 144	NR

Author, Year	Arms	N	Age	Female N (%)	Race N (%)	Smoking Status N (%)	Prior Stroke N (%)	Prior MI N (%)	Prior REVASC N (%)	DM N (%)	LDL	Between Group Differences
					27(11%) Hispanic: 23 (9.4%) Asian: 11 (4.5%) Arm 5: White: 162(65.6%) Black: 42(17%) Hispanic: 19 (7.7%) Asian: 15 (6.1%)							
Hamdan, 2011[27]	Arm 1: ATV 20 mg plus Placebo for 12 weeks Arm 2: ATV 10mg +Ezetimibe 10 mg for 12 weeks	Arm 1: 46 (49) Arm 2: 47 (51)	Arm 1: Mean: 58.9, SD: NR Arm 2: Mean: 60.9, SD: NR	NR	NR	NR	NR	NR	NR	NR	Arm 1: Mean: 3.4, SD: NR Arm 2: Mean: 3.2, SD: NR	NR
Her, 2013[28]	Arm 1: Atorva 20 mg Arm 2: Rosuva 10 mg Arm 3: Atorva/Ezetimibe 5/5 mg	Arm 1: 25 Arm 2: 25 Arm 3: 26	Arm 1: Mean: 63 SD: 9 Arm 2: Mean: 56 SD: 10 Arm 3: Mean: 59 SD: 11	Arm 1: 18 (72) Arm 2: 18 (72) Arm 3: 11 (58)	NR	Arm 1: 2 (8) Arm 2: 4 (16) Arm 3: 2 (8)	NR	CAD Arm 1: 0 (0) Arm 2: 0 (0) Arm 3: 0 (0)	NR	Arm 1: 0 (0) Arm 2: 0 (0) Arm 3: 0 (0)	Arm 1: Mean:168 SD: 15 Arm 2: Mean: 163 SD: 21 Arm 3: Mean: 165 SD: 20	NR

Author, Year	Arms	N	Age	Female N (%)	Race N (%)	Smoking Status N (%)	Prior Stroke N (%)	Prior MI N (%)	Prior REVASC N (%)	DM N (%)	LDL	Between Group Differences
Kawagoe, 2011[29]	Arm 1: FLV 60mg Arm 2: FLV 20mg +Ezetimibe10 mg	Arm 1: 12 Arm 2: 12	Arm 1: Mean: 65.1, SD: 7.2 Arm 2: Mean: 64.2, SD: 7.2	Arm 1: 7 Arm 2: 6	NR	NR	NR	NR	NR	Arm 1: 12 Arm 2: 10	Arm 1: Mean: 154, SD: 26 Arm 2: Mean: 164, SD: 33	NR
Kerzner, 2003[30]	Arm1: LOV 20mg Arm 2: LOV 40mg Arm 3: LOV10mg +Ezetimibe10 mg Arm 4: Placebo Arm 5: Ezetimibe 10mg Arm 6: LOV 10mg Arm 7: LOV 20mg +Ezetimibe 10mg Arm 8: LOV 40mg +Ezetimibe 10mg	*Placebo: 64 *Ezetimibe: 72 *All LOV: 220 *All Ezetimibe/LOV: 192 *Some arms are not eligible for our review	*Placebo Mean: 58 SD:12 *Ezetimibe: Mean:55 SD:11 *All LOV: Mean:56 SD:12 *All Ezetimibe/ LOV: Mean:57 SD:11	*Placebo: 40(63%) *Ezetimibe: 41(57%) *All LOV: 132(60%) *All Ezetimibe/ LOV: 106 (55%)	*Placebo White: 59(92%) Black: 2(3%) Hispanic: 2 (3%) *Ezetimibe: White: 60(83%) Black: 4(6%) Hispanic: 7(10%) *All LOV: White: 198(90%) Black: 14(6%) Hispanic: 8 (4%) *All Ezetimibe/ LOV: White: 167(87%) Black: 13(7%) Hispanic: 11 (6%)	*Placebo 8 (12%) *Ezetimibe: 7 (10%) *All LOV: 35 (16%) *All Ezetimibe/LOV: 21 (11%)	*Placebo 2 (3%) *Ezetimibe: 2 (3%) *All LOV: 21 (10%) *All Ezetimibe/ LOV: 13 (7%)	NR	NR	*Placebo 1 (2%) *Ezetimibe: 3(4%) *All LOV: 19(9%) *All Ezetimibe/ LOV: 12 (6%)	*Placebo Mean: 178 SD:3 *Ezetimibe: Mean:178 SD:2 *All LOV: Mean:178 SD:1 *All Ezetimibe/ LOV: Mean:176 SD: 1	None significant

Author, Year	Arms	N	Age	Female N (%)	Race N (%)	Smoking Status N (%)	Prior Stroke N (%)	Prior MI N (%)	Prior REVASC N (%)	DM N (%)	LDL	Between Group Differences
Lee, 2011[31]	Arm 1: ATV20 Arm 2: Z5/ Ezetimibe 5mg	Arm 1: 30 (50) Arm 2: 30 (50)	Arm 1: Mean: 62, SD: 9 Arm 2: Mean: 60, SD: 9	Arm 1: 21 (70) Arm 2: 20(67)	NR	Arm 1: Current:0 Arm 2: Current:2 (7)	NR	NR	NR	Arm 1: 2(7) Arm 2: 4(13)	Arm 1: Mean: 164, SD: 12 Arm 2: Mean: 163, SD: 23	NR
Lee, 2012[32]	Arm 1: ATV 20 mg Arm 2: ATV 5mg +Ezetimibe 5mg	Arm 1: 28 Arm 2: 32	Arm 1: Mean: 63, SD: 8 Arm 2: Mean: 62, SD: 12	Arm 1: 18(64) Arm 2: 16 (50)	NR	Arm 1: Current: 2 (8), Current/Never %: NR Arm 2: Current: 2 (6), Current/Never %:NR	NR	NR	NR	Arm 1: 2 (7) Arm 2: 3 (9)	Arm 1: Mean: 161, SD: 16 Arm 2: Mean: 159, SD: 12	NR
Lee, 2013[33]	Arm 1: ATV 20 mg Arm 2: Ezetimibe/SMV 10/20	Arm 1: 66 Arm 2: 66	Arm 1: Mean: 64, SD: 7.7 Arm 2: Mean: 65, SD: 7.6	Arm 1: 32(49) Arm 2: 40 (60)	NR	NR	Arm 1: 1(1.5) Arm 2: 4 (6.1)	CAD Arm 1: 20(30) Arm 2: 21 (32)	NR	Arm 1: 66(100) Arm 2: 66 (100)	Arm 1: Mean: 134, SD: 30 Arm 2: Mean: 139, SD: 27	NR
Liberopoulos, 2013[34]	Arm 1: SMV 40 mg Arm 2: SMV 10mg + Ezetimibe10mg	Arm 1: 25 (50%) Arm 2: 25 (50%)	Arm 1: Mean: 58, SD: 8 Arm 2: Mean: 54, SD: 12	Arm 1: 14 Arm 2: 13	Arm 1: Specific: 25 (100) Arm 2: Specific: 25 (100)	Arm 1: Current: NR (38), Current/Never %: NR Arm 2: Current:NR (41), Current/Never %:NR	NR	NR	NR	NR	Arm 1: Mean: 177, SD: 32 Arm 2: Mean: 176, SD: 48	NR
Matsue, 2013[35]	Arm 1: ATV 20 mg	Arm 1: 128	Arm 1: Mean: 70.3,	Arm 1: 32(25)	NR	Arm 1: Current: 22(17.2),	Arm 1: 8(6.2)	Arm 1: 79(62)	Arm 1: 102(79.7)	Arm 1: 52(41)	Arm 1: Mean: 95, SD: 18	NR

Author, Year	Arms	N	Age	Female N (%)	Race N (%)	Smoking Status N (%)	Prior Stroke N (%)	Prior MI N (%)	Prior REVASC N (%)	DM N (%)	LDL	Between Group Differences
	Arm 2: Ezetimibe/SMV 10/10	Arm 2: 115	SD: 9.9 Arm 2: Mean: 69.2, SD: 9.3	Arm 2: 32 (28)		Arm 2: Current:20 (17.4),	Arm 2: 4 (3.5)	Arm 2: 70 (60.9)	Arm 2: 85 (73.9)	Arm 2: 42 (37)	Arm 2: Mean:94, SD: 17	
McKenney, 2007[36]	Arm1: RSV 20 mg Arm 2: SMV 20mg +Ezetimibe10 mg	Arm1: RSV20 mg:73 Arm 2: SMV20 mg/Ezetimibe 10mg: 72 *Arm3: ATV/N-ER (40/2000): 60 *Arm4: RSV/N-ER (20/1000): 65	Arm 1: Mean: 57 SD: 11 Arm 2: Mean: 59 SD: 10 Arm 3: Mean: 59 SD: 12 Arm4: Mean: 58 SD: 11	Arm 1: (48%) Arm 2: (47%) Arm 3: (52%) Arm 3: (52%)	Arm 1: White: (84%) Arm 2: White: (87%) Arm 3: White: (79%) Arm 4: White: (90%)	Arm 1: (18%) Arm 2: (17%) Arm 3: (22%) Arm 4: (11%)	NR	NR	NR	NR	Arm 1: Mean: 198 SD: 34 Arm 2: Mean: 202 SD: 44 Arm 3: Mean: 195 SD: 43 Arm 4: Mean: 194 SD: 37	None
Moutzouri, 2011[37]	Arm 1: Open-label SMV 40 mg for 12 weeks Arm 2: RSV 10mg Arm 3: Open-label SMV10mg	Arm 1: 55 (36) Arm 2: 45 Arm 3: 53 (35)	Arm 1: Mean: 58, SD: 8 Arm 2: Arm 3: Mean: 60, SD:	Arm 1: 37(67) Arm 2: NR Arm 3: 32 (60)	NR	Arm 1: Current: NR (6), Former: NR, Current/Former: NR, Never: NR Arm 2: NR Arm 3: Current: NR (6),	NR	NR	NR	Arm 1: N: 0 (0) Arm 2: NR Arm 3: N: 0 (0)	Arm 1: Mean: 176, SD: 34 Arm 2: NR Arm 3: Mean: 177, SD: 33	NR

Author, Year	Arms	N	Age	Female N (%)	Race N (%)	Smoking Status N (%)	Prior Stroke N (%)	Prior MI N (%)	Prior REVASC N (%)	DM N (%)	LDL	Between Group Differences
	+Ezetimibe 10 mg for 12 weeks		8			Former: NR, Current/Former: NR, Never: NR						
Moutzouri, 2012[38]	Arm 1: SMV 80mg Arm 2: SMV 10mg +Ezetimibe 10mg	Arm 1: 30 Arm 2: 30	Arm 1: Mean: 56.9, SD: 13 Arm 2: Mean: 56.9, SD: 11	Arm 1: 14 Arm 2: 18	NR	Arm 1: Current: 10, Current/Never %:NR Arm 2: Current: 10, Current/Never% :NR	NR	NR	NR	NR	Arm 1: Mean: 174, SD: 41 Arm 2: Mean: 179, SD: 26	NR
Okada, 2011[39]	Arm 1: ATV 20 mg Arm 2: RSV 5 mg Arm 3: ATV 10mg +Ezetimibe 10mg Arm 4: RSV 2.5mg +Ezetimibe 10 mg	Arm 1: 35 (21.2) Arm 2: 38 (23.0) Arm 3: 43 (26.1) Arm 4: 49 (30.0)	Arm 1: Mean: 65, SD: 9 Arm 2: Mean: 68, SD: 7 Arm 3: Mean: 66, SD: 8 Arm 4: Mean: 66, SD: 11	Arm 1: 6(17.1) Arm 2: 12 (31.6) Arm 3: 15(35.0) Arm 4: 12 (24.5)	NR	Arm 1: Current: 11 (31), Current/Never %:NR Arm 2: Current: 15 (39), Current/Never %:NR Arm 3: Current: 14 (33), Current/Never %: NR Arm 4: Current: 25 (51), Current/Never %: NR	Arm 1: N: 1 (3) Arm 2: N: 0 (0) Arm 3: N: 1 (2) Arm 4: N: 0 (0)	Arm 1: N: 16 (46) Arm 2: N: 22 (58) Arm 3: N: 26 (60) Arm 4: N: 25 (51)	NR	Arm 1: N: 19 (54) Arm 2: N: 18 (47) Arm 3: N: 17 (40) Arm 4: N: 27 (55)	Arm 1: Mean: 114.1 SD: 14.7 Arm 2: Mean:120.3 SD: 18.4 Arm 3: Mean:120.5 SD: 16.9 Arm 4: Mean: 120.0, SD: 13.1	NR
Ostad, 2009[40]	Arm 1: ATV 80mg Arm 2: ATV 10mg + Ezetimibe	Arm 1: 24 Arm 2: 25	Arm 1: Mean: 66, SD: 9 Arm 2:	Arm 1: N: 5 (21) Arm 2: 6 (24)	NR	Arm 1: Current: 4 (17), Former: NR, Current/Former: NR, Never: NR	NR	NR	NR	Arm 1: 6 (25) Arm 2: 4 (16)	Arm 1: Mean: 148, SD: 31 Arm 2: Mean: 151,	NR

Author, Year	Arms	N	Age	Female N (%)	Race N (%)	Smoking Status N (%)	Prior Stroke N (%)	Prior MI N (%)	Prior REVASC N (%)	DM N (%)	LDL	Between Group Differences
	10mg		Mean: 64, SD: 10			Arm 2: Current: 8 (32), Former: NR, Current/Former: NR, Never: NR					SD: 31	
Pesaro, 2012[41]	Arm 1: SMV 80mg Arm 2: SMV 20mg +Ezetimibe 10mg	Arm 1: 38 Arm 2: 40	Arm 1: Median: 61.7, SD: 10 Arm 2: Median: 64.5, SD: 9	Arm 1: NR(45) Arm 2: NR(32)	NR	Arm 1: Current: 8 (23), Current/Never %: NR Arm 2: Current: 5 (13), Current/Never %: NR	Arm 1: 3(8) Arm 2: 3 (8)	Arm 1: 29(76) Arm 2: 24(60)	Arm 1: 16(42) Arm 2: 16(40)	Arm 1: 20 (52) Arm 2: 16 (40)	Arm 1: Mean: 101, SD: NR Arm 2: Mean: 99, SD: NR	NR
Piorkowski, 2007[42]	Arm1: ATV 40mg Arm 2: ATV 10mg +Ezetimibe 10mg	Arm 1: 25 Arm 2: 26	Arm 1: Mean:61.4 SD:1.8 Arm 2: Mean:62.0 SD:2.1	Arm 1: 3(12) Arm 2: 6(23.1)	NR	Arm 1: 16(64) Arm 2: 18(69)	51(100)	NR	NR	Arm 1: 7(28) Arm 2: 4(15.4)	Arm 1: Mean:3.49 SD:0.18 mmol/l Arm 2: Mean:3.61 SD:0.22 mmol/l	No significant difference
Robinson, 2009[43]	Arm 1: ATV 10mg Arm 2: SMV 20mg +Ezetimibe 10mg Arm 3: ATV 20mg Arm 4: SMV 40mg +Ezetimibe 10mg Arm 5:	Arm 1: 229 Arm 2: 229 Arm 3: 229 Arm 4: 228 Arm 5: 228	Arm 1: Mean: 60, SD: 10 Arm 2: Mean: 60, SD: 9 Arm 3: Mean: 58, SD: 10 Arm 4: Mean: 60, SD: 10	Arm 1: 97 (42) Arm 2: 87 (38) Arm 3: 106 (46) Arm 4: 104 (46) Arm 5: 104 (46)	Arm 1: White: 172 (75), Black: 13 (6), Latino: NR, Asian: 17 (7), Mixed: NR, Specific: 27 (12) Arm 2: White: 169 (74), Black: 18 (8), Latino: NR, Asian:	NR	NR	Arm 1: 49(21) Arm 2: 45(20) Arm 3: 39(17) Arm 4: 48(21) Arm 5: 42(18)	NR	Arm 1: 122(53) Arm 2: 113 (49) Arm 3: 125(55) Arm 4: 123(54) Arm 5: 134(59)	Arm 1: Mean: 142, SD: 40 Arm 2: Mean: 137, SD: 33 Arm 3: Mean: 139, SD: 33 Arm 4: Mean: 134, SD: 28 Arm 5: Mean: 140,	NR

Author, Year	Arms	N	Age	Female N (%)	Race N (%)	Smoking Status N (%)	Prior Stroke N (%)	Prior MI N (%)	Prior REVASC N (%)	DM N (%)	LDL	Between Group Differences
	ATV 40mg		Arm 5: Mean: 58, SD: 10		15 (7), Mixed: NR, Specific: 27 (12) Arm 3: White: 177 (77), Black: 18 (8), Latino: NR, Asian: 15 (7), Mixed: NR, Specific: 18 (8) Arm 4: White: 171 (75), Black: 12 (5), Latino: NR, Asian: 18 (8), Mixed: NR, Specific: 27 (12) Arm 5: White: 167 (73), Black: 14 (6), Latino: NR, Asian: 21 (9), Mixed: NR, Specific: 14 (6)						SD: 33	
Roeters van Lennep, H.W.O, 2007[44]	Arm1: SMV 40mg (with SMV 20mg during run in)	Arms 1&2: 189 Arms	Arms 1&2: Mean: 65 SD:10	Arms 1&2: 45(24%) Arms 3&4: 44	NR	NR	Arms 1&2: 184 (97%)	NR	NR	Arms 1&2: 25(13%) Arms	Arms 1&2: Mean: 3.2 SD: 05 Arms 3&4:	None

Author, Year	Arms	N	Age	Female N (%)	Race N (%)	Smoking Status N (%)	Prior Stroke N (%)	Prior MI N (%)	Prior REVASC N (%)	DM N (%)	LDL	Between Group Differences
	Arm 2: ATV 20mg (with ATV10mg during run in) Arm 3: SMV20 +Ezetimibe 10mg (with SMV 20 during run in) Arm 4: SMV 20mg +Ezetimibe 10mg (with ATV 10mg during run in)	3&4: 178	Arms 3&4: Mean:64 SD:10	(25%)			Arms 3&4: 173 (97%)			3&4: 20 (11%)	Mean: 3.1 SD:0.5 *LDL in mmol/L	
Rudofsky, 2012[45]	Arm 1: SMV 80mg Arm 2: SMV 10mg +Ezetimibe 10mg Arm 3: Placebo	Arm 1: 10 Arm 2: 11 Arm 3: 9	Arm 1: Mean: 56, SD: 10 Arm 2: Mean: 65, SD: 9 Arm 3: Mean: 64, SD: 9	Arm 1: 6 Arm 2: 6 Arm 3: 7	NR	NR	NR	NR	NR	Arm 1: (100) Arm 2: (100) Arm 3: (100)	Arm 1: Mean: 145, SD: 19 Arm 2: Mean: 147, SD: 32 Arm 3: Mean: 143, SD: 45	Arm 1: NR Arm 2: Mean age (p=0.04) higher; diastolic BP lower (p=0.005) Arm 3: NR
Stein, E, 2004[46]	Arm1: ATV 20mg Arm 2: ATV 10mg +Ezetimibe	Arm 1: 316 Arm 2: 305	Arm 1: Mean: 51.6 Range: 18-80	Arm 1: 145(46%) Arm 2: 146(48%)	Arm 1: White: 289 (91%) Non-white: 27(9%)	Arm 1: Current; 85 (27%) Arm 2: Current:76	Arm 1: 100(32%) Arm 2: 90(30%	NR	Arm 1: 54(17%) Arm 2: 43(14%)	Arm 1: 23(7%) Arm 2: 19(6%)	*Arm 1: Mean: 187.3 SD:2.6 Arm 2:	No significant differences

Author, Year	Arms	N	Age	Female N (%)	Race N (%)	Smoking Status N (%)	Prior Stroke N (%)	Prior MI N (%)	Prior REVASC N (%)	DM N (%)	LDL	Between Group Differences
	10mg		Arm 2: Mean:53.0 Range: 18-82		Arm 2: White: 279(91%) Non-white: 26(9%)	(25%)	)				Mean: 186.2 SD: 2.7 *Direct LDL-c	
Yamazaki, 2013[47]	Arm 1: RSV 10 mg Arm 2: RSV2.5mg +Ezetimibe 10mg	Arm 1: 24 Arm 2: 22	Arm 1: Mean: 71.8, SD: 8.2 Arm 2: Mean: 70.1, SD: 9.6	Arm 1: 9(37.5) Arm 2: 8 (36.4)	NR	Arm 1: Current/Former: 15 (62.5), Never %: NR Arm 2: Current/Former: 11 (50), Never %: NR	NR	NR	NR	Arm 1: N: 10 (41.7) Arm 2: N: 8 (36.4)	Arm 1: Mean: 88.5, SD: 12.9 Arm 2: Mean: 84.3, SD: 14.5	NR
Zieve, 2010[48] Ben-Yehuda, 2011[49]	Arm 1: ATV 20mg Arm 3: ATV 10mg + Ezetimibe 10mg	Arm 1: 527 Arm 3: 526	Arm 1: Mean: 71, SD: 5 Arm 3: Mean: 71, SD: 5	Arm 1: 286 (54) Arm 3: 277 (53)	Arm 1: White: 505 (96), Black: 17 (3), Latino: NR, Asian: NR, Mixed: NR, Specific: 5 (1) Arm 3: White: 503 (96), Black: 21 (4), Latino: NR, Asian: NR, Mixed: NR, Specific: 2 (<1)	NR	NR	Arm 1: 423 (80) Arm 3: 418 (80)	NR	Arm 1: 113 (21) Arm 3: 110 (21)	Arm 1: Mean: 101, SD: 21 Arm 3: Mean: 103, SD: 28	NR

AVD atherosclerotic vascular disease; ATV atorvastatin; SMV simvastatin; CHD Coronary Heart Disease; FLV fluvastatin LDL low density lipoprotein; LOV lovastatin; MI myocardial infarction; NR not reported; REVASC revascularization; RSV rosuvastatin

Evidence Table E11. Mortality – general population

RefID	Arm	Outcome Units	Baseline N	Baseline Outcome	Timepoint(s)	N at Timepoint(s)	Outcomes at Timepoint(s)	Within Arm Comparisons	Between arm comparison
***Low* potency statin combination therapy versus *high* potency statin monotherapy**									
Bays, 2004 [50]	SMV 40 mg	Mortality-cardiac arrest	NR	N/A	12 weeks	NR	N=0	NR	NR
Bays, 2004 [50]	SMV 80 mg	Mortality-cardiac arrest	NR	N/A	12 weeks	NR	N=0	NR	NR
Bays, 2004 [50]	EZE/SMV 10/10 mg	Mortality-cardiac arrest	NR	N/A	12 weeks	NR	N=0	NR	NR
Davidson, 2002 [18]	SMV 80 mg	Mortality	63	NR	12 weeks	NR	N=0	NR	NR
Davidson, 2002 [18]	SMV 40 mg	Mortality	60	NR	12 weeks	NR	N=0	NR	NR
Davidson, 2002 [18]	EZE/SMV 10/10 mg	Mortality	61	NR	12 weeks	NR	N=0	NR	NR
***Mid* potency statin combination therapy versus *high* potency statin monotherapy**									
Bays, 2004 [50]	SMV 40 mg	Mortality-cardiac arrest	NR	NR	12 weeks	NR	N=0	NR	NR
Bays, 2004 [50]	SMV 80 mg	Mortality-cardiac arrest	NR	NR	12 weeks	NR	N=0	NR	NR
Bays, 2004 [50]	EZE/SMV 10/20 mg	Mortality-cardiac arrest	NR	NR	12 weeks	NR	N=1	NR	NR
Catapano, 2006 [15]	RSV 40 mg	Mortality	494	NR	6 weeks	NR	% with event=0	NR	NR
Catapano, 2006 [15]	RSV 20 mg	Mortality	495	NR	6 weeks	NR	% with event=0	NR	NR

Catapano, 2006 [15]	RSV 10 mg	Mortality	492	NR	6 weeks	NR	% with event=0	NR	NR
Catapano, 2006 [15]	EZE 10/SMV 20 mg	Mortality	492	NR	6 weeks	NR	% with event=0	NR	NR
Davidson, 2002 [18]	SMV 80 mg	Mortality	63	NR	12 weeks	NR	N=0	NR	NR
Davidson, 2002 [18]	SMV 40 mg	Mortality	60	NR	12 weeks	NR	N=0	NR	NR
Davidson, 2002 [18]	SMV 20/EZE 10 mg	Mortality	58	NR	12 weeks	NR	N=1	NR	NR
Foody, 2010 [21]	ATV 20mg	Mortality	259	NR	12 weeks	258	N with events: 1, %with events: 0.4 ,	NR	NR
Foody, 2010 [21]	ATV 40mg	Mortality	257	NR	12 weeks	256	N with events: 0, %with events: 0 ,	NR	NR
Foody, 2010 [21]	EZE10/ SMV20 mg	Mortality	259	NR	12 weeks	256	N with events:1, %with events:0.4 ,	NR	NR
Robinson, 2009[43]	ATV 20mg	Mortality	229	NR	6 weeks	NR	Count: 0	NR	NR
Robinson, 2009[43]	ATV 40mg	Mortality	228	NR	6 weeks	NR	Count: 0	NR	NR
Robinson, 2009[43]	SMV 20 +EZE 10mg	Mortality	229	NR	6 weeks	NR	Counts: 0	NR	Difference (95%CI)=0.0 (-0.6, 0.9)
Zieve, 2010[48] Ben-Yehida, 2011[49]	ATV 20/40mg	Mortality	527	NR	12 weeks	525	%: <1, N with events: 1 ,	NR	NR
Zieve, 2010[48] Ben-Yehida, 2011[49]	ATV 10mg + EZE10mg	Mortality	526	NR	12 weeks	526	%: <1, N with events: 2 ,	NR	NR
***Low* potency statin combination therapy versus *mid* potency statin monotherapy**									

Bays, 2004 [50]	SMV 20 mg	Mortality-cardiac arrest	NR	NR	12 weeks	604	N=0	NR	NR
Bays, 2004 [50]	Arm 4: EZE/SMV 10/10 mg	Mortality-cardiac arrest	NR	NR	12 weeks	NR	N=0	NR	NR
Davidson, 2002 [18]	SMV 10/EZE 10 mg	Mortality	61	NR	12 weeks	NR	N=0	NR	NR
Davidson, 2002 [18]	SMV 20 mg	Mortality	53	NR	12 weeks	NR	N=0	NR	NR

ATV atorvastatin; EZE Ezetimibe; SMV simvastatin; NR not reported

Evidence Table E12. Acute coronary events – general population

Author, Year	Arm	Outcome Units	Baseline N	Baseline Outcome	Timepoint (s)	N at Timepoint(s)	Outcomes at Timepoint(s)	Within Arm Comparisons	Between Arm Comparisons
***Mid* potency statin combination therapy versus *high* potency statin monotherapy**									
Stein, 2004[46]	ATV 20	Fatal MI	316	NR	14 weeks	303	N:1	NR	NR
Stein, 2004[46]	ATV 10mg +EZE10mg	Fatal MI	305	NR	14 weeks	293	N: 0	NR	NR

ATV atorvastatin; EZE Ezetimibe; MI Myocardial infarction; NR not reported

Evidence Table E13. Serious adverse events – general population

Author, Year	Arm	Outcome Units	Baseline N	Baseline Outcome	Timepoint (s)	N at Timepoint(s)	Outcomes at Timepoint(s)	Within Arm Comparisons	Between Arm Comparisons
***Mid* potency statin combination therapy versus *high* potency statin monotherapy**									
Foody, 2010[21]	ATV 20mg	Serious Adverse Events	259	NR	12 weeks	258	N(%)of with events: 3(1.2),	NR	NR
Foody, 2010[21]	ATV 40mg	Serious Adverse Events	257	NR	12 weeks	256	N(%)with events: 5(2)	NR	NR
Foody, 2010[21]	SMV 20mg +EZE 10mg	Serious Adverse Events	259	NR	12 weeks	256	N(%) with events: 8(3.1)	NR	NR
Stein, 2004[46]	ATV 20mg	Serious Adverse Events	316	NR	14 weeks	316	N(%)with events:9 (3)	NR	NR
Stein, 2004[46]	ATV 10mg +EZE10mg	Serious Adverse Events	305	NR	14 weeks	305	N(%)with events:12(4)	NR	NR
Zieve, 2010[48] Ben-Yehida, 2011[49]	ATV 20/40mg	Serious Adverse Events	527	NR	12 weeks	525	N(%) with events: 14(3)	NR	NR
Zieve, 2010[48] Ben-Yehida, 2011[49]	ATV10mg + EZE10mg	Serious Adverse Events	526	NR	12 weeks	526	N(%) with events: 15 (3)	NR	NR
***Low* potency statin combination therapy versus *mid* potency statin monotherapy**									
Feldman, 2004[19]	SMV 20mg	Serious Adverse Events	253	NR	23 weeks	303	N(%)with events:12(4.7)	NR	NR
Feldman, 2004[19]	SMV 10mg +EZE 10mg	Serious Adverse Events	251	NR	23 weeks	293	N(%)with events:20(8.0)	NR	NR

ATV atorvastatin; EZE Ezetimibe; SMV simvastatin; NR not reported

Evidence Table E14. LDLc outcome – general population

Author, Year	Arm	Outcome Units	Baseline N	Baseline Outcome	Timepoint (s)	N at Timepoint (s)	Outcomes at Timepoint(s)	Within Arm Comparisons	Between Arm Comparison
Low potency statin in combination with EZE as compared to high potency statin monotherapy in general populations									
Ahmed, 2008[8]	ATV 20mg	LDLc mg/dl	111	Mean: 179	6 weeks	NR	NR	Mean% reduction: -44.40(reported, not calculated)	NR
Ahmed, 2008[8]	SMV 10mg +EZE10mg	LDLc mg/dl	108	Mean: 180	6 weeks	NR	NR	Mean %reduction: -56.10 (reported, not calculated)	NR
Araujo, 2010[9]	SMV 80	LDLc mg/dl, calculated	12	Mean:205.78, SD: 41.96	4weeks	12	Mean: 100.95, SD: 28.07	% change;-49.05 p:0.162	NR
Araujo, 2010[9]	Arm 2: SMV 10mg +EZE10mg	LDLc mg/dl ,	11	Mean:200.69, SD: 42.83	4weeks	11	Mean: 109.83, SD: 37.33,	% change;-45.27 P < 0.001	NR
Ballantyne, 2004[12]	ATV 20mg	Continuous LDLc mg/dl	230	Mean:178.2 SD: 38.7	6 weeks	230	NR	% Change from baseline: -43.7	NR
Ballantyne, 2004[12]	ATV 40mg	Continuous LDLc mg/dl	232	Mean: 179.7 SD: 38.1	6 weeks	232	NR	% Change from baseline: -48.3	NR
Ballantyne, 2004[12]	ATV 80mg	Continuous LDLc mg/dl	230	Mean: 182.7 SD:38.3	6 weeks	230	NR	% Change from baseline: -52.9	NR
Ballantyne, 2004[12]	SMV 10mg +EZE10mg	Continuous LDLc mg/dl	230	Mean: 176.7 SD: 33.0	6 weeks	230	NR	% Change from baseline: -47.1	NR
Bays, 2004[50]	Arm 2: SMV 40mg	Continuous LDLc mg/dl	NR	NR	12 weeks	150-154	NR	-40.6	NR

Author, Year	Arm	Outcome Units	Baseline N	Baseline Outcome	Timepoint (s)	N at Timepoint (s)	Outcomes at Timepoint(s)	Within Arm Comparisons	Between Arm Comparison
		calculated							
Bays, 2004[50]	SMV 80mg	Continuous LDLc mg/dl calculated	NR	NR	12 weeks	150-156	NR	-48.5	NR
Bays, 2004[50]	SMV 10mg +EZE10mg	Continuous LDLc mg/dl calculated	NR	NR	12 weeks	140-151	NR	-44.8	NR
Davidson, 2002[18]	SMV 40mg	Continuous LDLc mg/dl calculated	65	NR	12 weeks	60	NR	Mean% change from baseline: -36	NR
Davidson, 2002[18]	SMV 80mg	Continuous LDLc mg/dl calculated	67	NR	12 weeks	63	NR	Mean% change from baseline: -44	NR
Davidson, 2002[18]	SMV 10 +EZE10mg	Continuous LDLc mg/dl calculated	67	NR	12 weeks	61	NR	Mean% change from baseline: -44	NR
Florentin, 2011[20]	SMV 40mg	LDLc mg/dl , calculated	50	Mean: 172, SD: 31	3months	50	Mean: 97, SD: 23	% change from baseline: -43, p<0.0001	NR
Florentin, 2011[20]	SMV 10 +EZE10mg	LDLc mg/dl	50	Mean: 178, SD: 31	3months	50	Mean: 90, SD: 20	% change from baseline:-49, p<0.0001	p: <0.05 , comparing monotherapy vs. combination at 3 months

Author, Year	Arm	Outcome Units	Baseline N	Baseline Outcome	Timepoint (s)	N at Timepoint (s)	Outcomes at Timepoint(s)	Within Arm Comparisons	Between Arm Comparison
Goldberg, 2004[23]	SMV 40mg	Continuous LDLc mg/dl calculated	NR	NR	12 weeks	90	NR	Mean% change from baseline: -41.5 IQR: -40, -50	NR
Goldberg, 2004[23]	SMV 80mg	Continuous LDLc mg/dl calculated	NR	NR	12 weeks	87	NR	Mean% change from baseline: -45.6 IQR: -41.5, -57	NR
Goldberg, 2004[23]	SMV10mg +EZE10mg	Continuous LDLc mg/dl calculated	NR	NR	12 weeks	87	NR	Mean% change from baseline: -46.2 IQR: -42,-57	p<0.001 vs. SMV 40 mg
Her, 2013 [28]	ATV/EZE 5/5 mg	LDLc mg/dl	26	Mean: 165 SD:20	8 weeks	26	Mean:81 SD:14	% change= -50 SD= 8 P<0.001	NR
Her, 2013 [28]	ATV 20 mg	LDLc mg/dl	25	Mean:168 SD:15	8 weeks	25	Mean:92 SD:24	% change= -45 SD= 12 P<0.001	P=0.22 (ANOVA)
Lee, 2011[31]	ATV 20mg	LDLc mg/dl ,	30	Mean: 164, SD: 12,	8 weeks	30	Mean: 87, SD: 23	% change from baseline= -47%, p<0.001	NR
Lee, 2011[31]	ATV 5mg +EZE 5mg	LDLc mg/dl ,	30	Mean: 163, SD: 23,	8 weeks	30	Mean: 82, SD: 14	% change from baseline:-49%, p<0.001	p: 0.40 comparing monotherapy vs. combination at 8 weeks
Lee,	ATV 20mg	LDLc	28	Mean: 161	8weeks	28	Mean: 105,	% change from	NR

Author, Year	Arm	Outcome Units	Baseline N	Baseline Outcome	Timepoint (s)	N at Timepoint (s)	Outcomes at Timepoint(s)	Within Arm Comparisons	Between Arm Comparison
2012[32]		mg/dl		SD: 16,			SD: 38, ,	baseline:-35 (calculated), net mean difference:-56, p<0.001	
Lee, 2012[32]	ATV 5mg +EZE5mg	LDLc mg/dl	32	Mean: 159 SD: 12	8weeks	32	Mean: 90, SD: 26, ,	% change from baseline: -43 (calculated), net mean difference:-69, p<0.001	p: 0.12, comparing monotherapy vs. combination at 8 weeks
Liberopoulos, 2013[34]	SMV 40mg	LDLc , mg/dL, calculated	25	Mean: 176, SD: 48	3 months	25	Mean: 97, SD: 28	% mean change from baseline: -44.8, p=0.000	NR
Liberopoulos, 2013[34]	SMV 10mg +EZE10mg	LDLc ,	25	Mean: 177, SD: 32	3 months	25	Mean: 92, SD: 19	% mean change from baseline: -48.0, p=0.000	NR
Moutzouri, 2011[37]	SMV 40mg	LDLc mg/dl, calculated	55	Mean: 176, SD: 34	12 weeks	55	Mean: 99, SD: 26	%change from baseline (calculated, not reported) :-43.8 p<0.001 Week 12 vs. week 0	NR
Moutzouri, 2011[37]	RSV 10mg	LDLc mg/dl	45	Mean: 182, SD: 33	12weeks	45	Mean: 99, SD: 24	% change from baseline (calculated, not reported) : -45.6 p<0.001 Week 12 vs. 0	NR
Moutzouri, 2011[37]	RSV 10mg	LDLc mg/dl	45	Mean: 61 SD: 13	12 weeks	45	Mean: 63 SD: 14	p= ns 0 weeks vs. 12 weeks	
Moutzouri, 2011[37]	SMV10mg +EZE10mg	LDLc mg/dl	53	Mean: 177, SD: 33	12weeks	53	Mean: 91, SD: 20	% change from baseline (calculated, not reported) : -48.6	P=NS comparing all arms at 12 weeks

Author, Year	Arm	Outcome Units	Baseline N	Baseline Outcome	Timepoint (s)	N at Timepoint (s)	Outcomes at Timepoint(s)	Within Arm Comparisons	Between Arm Comparison
								p<0.001 Week 12 vs. week 0	Mean Diff =NR SD=NR SE=NR
Moutzouri, 2012[38]	SMV 80mg	LDLc mg/dl , calculated	30	Mean: 174, SD: 41	12 weeks	30	Mean: 96, SD: 33	% mean change from baseline: -44.8(calculated, not reported), p<0.001 Week 12 vs. week 0	NR
Moutzouri, 2012[38]	SMV10mg +EZE10mg	LDLc mg/dl , calculated	30	Mean: 179, SD: 26	12 weeks	30	Mean: 91, SD: 15	% mean change from baseline:-49.2 (calculated, not reported) p:<0.001 Week 12 vs. week 0	NR
Mid ***potency statin combination therapy versus*** ***high*** ***potency statin monotherapy***									
Ballantyne 2003[11]	ATV 20mg	Continuous LDLc measured	NR	NR	12 weeks	NR	NR	% mean change from baseline: -40	p<0.01, vs. ATV 80
Ballantyne 2003[11]	ATV 40mg	Continuous LDLc measured	NR	NR	12 weeks	NR	NR	% mean change from baseline: -43	NR
Ballantyne 2003[11]	ATV 80mg	Continuous LDLc measured	NR	NR	12 weeks	NR	NR	% mean change from baseline: -51	NR
Ballantyne 2003[11]	ATV10mg +EZE10mg	Continuous LDLc measured	NR	NR	12 weeks	NR	NR	% mean change from baseline: -50	p<0.01, vs. ATV 20; p<0.01, vs. ATV 80;

Author, Year	Arm	Outcome Units	Baseline N	Baseline Outcome	Timepoint (s)	N at Timepoint (s)	Outcomes at Timepoint(s)	Within Arm Comparisons	Between Arm Comparison
Ballantyne, 2004[12]	ATV 20mg	Continuous LDLc mg/dl	230	Mean:178.2 SD: 38.7	6 weeks	230	NR	% Change from baseline: -43.7	NR
Ballantyne, 2004[12]	ATV 40mg	Continuous LDLc mg/dl	232	Mean: 179.7 SD: 38.1	6 weeks	232	NR	% Change from baseline: -48.3	NR
Ballantyne, 2004[12]	ATV 80mg	Continuous LDLc mg/dl	230	Mean: 182.7 SD:38.3	6 weeks	230	NR	% Change from baseline: -52.9	NR
Ballantyne, 2004[12]	SMV 20mg +EZE10mg (M)	Continuous LDLc mg/dl	233	Mean: 178.5 SD: 43.5	6 weeks	233	NR	% Change from baseline: -50.6	NR
Bays, 2004[50]	SMV 40mg	Continuous LDLc mg/dl calculated	NR	NR	12 weeks	150-154	NR	Mean% change from baseline: -40.6	NR
Bays, 2004[50]	SMV 80mg	Continuous LDLc mg/dl calculated	NR	NR	12 weeks	150-156	NR	Mean% change from baseline: -48.5	NR
Bays, 2004[50]	SMV 10mg +EZE20mg	Continuous LDLc mg/dl calculated	NR	NR	12 weeks	140-153	NR	-51.9	NR
Catapano, 2006[15]	RSV 10mg	LDL mg/dl calculated	475	Mean:172	6 weeks	475	NR	Least squares mean %change from baseline(SE):-	NR

Author, Year	Arm	Outcome Units	Baseline N	Baseline Outcome	Timepoint (s)	N at Timepoint (s)	Outcomes at Timepoint(s)	Within Arm Comparisons	Between Arm Comparison
								45.8(0.5)	
Catapano, 2006[15]	RSV 20mg	LDL mg/dl calculated	478	Mean:173	6 weeks	478	NR	Least squares mean %change from baseline(SE):-52.3(0.5)	NR
Catapano, 2006[15]	RSV 40mg	LDL mg/dl calculated	475	Mean:173	6 weeks	475	75	Least squares mean% change from baseline(SE):-56.7(0.5)	NR
Catapano, 2006[15]	SMV20mg +EZE10mg	LDL mg/dl calculated	476	Mean:172	6 weeks	476	84	Least squares mean % change from baseline(SE):-51.5(0.5)	NR
Davidson, 2002[18]	SMV 40mg	NR	65	NR	12 weeks	60	NR	Mean% change from baseline: -36	NR
Davidson, 2002[18]	SMV 80mg	NR	67	NR	12 weeks	63	NR	Mean% change from baseline: -44	NR
Davidson, 2002[18]	SMV 20mg +EZE10mg	NR	69	NR	12 weeks	58	NR	Mean% change from baseline: -45	NR
Foody, 2010[21]	ATV 20mg	LDLc mg/dl , All participants	248-257	Mean: 165, SD: 29	12 weeks	238	NR	% change from baseline= -46.6%	NR
Foody, 2010[21]	ATV 40mg	LDLc mg/dl , All participants	245-256	Mean: 168, SD: 30	12 weeks	239	NR	% change from baseline: -50.8%	NR
Foody, 2010[21]	SMV 20mg +EZE10mg	LDLc mg/dl , All participants	253-258	Mean: 166, SD: 30	12 weeks	232	NR	% change from baseline:-54.2	p: <0.001 N Analyzed:470, Diff.Least

Author, Year	Arm	Outcome Units	Baseline N	Baseline Outcome	Timepoint (s)	N at Timepoint (s)	Outcomes at Timepoint(s)	Within Arm Comparisons	Between Arm Comparison
									Squares Mean: -7.5 comparing SMV/EZE vs. ATV 20 mg at 12 weeks
Goldberg, 2004[23]	SMV 40mg	Continuous LDLc mg/dl calculated	NR	NR	12 weeks	90	NR	Mean% change from baseline: -41.5 IQR: -40, -50	NR
Goldberg, 2004[23]	SMV 80mg	Continuous LDLc mg/dl calculated	NR	NR	12 weeks	87	NR	Mean% change from baseline: -45.6 IQR: -41.5, -57	NR
Goldberg, 2004[23]	SMV20mg +EZE10mg	Continuous LDLc mg/dl calculated	NR	NR	12 weeks	86	NR	Mean% change from baseline: -50.5 IQR:-45, -63	p<0.001 vs. SMV 40 p<0.001 vs. SMV 80
McKenney, 2007[36]	RSV 20 mg	Continuous LDLc mg/dl calculated	73	Mean:198 SD: 34	8 weeks	NR	NR	% Change from baseline: %: -50 95% CI: -53,-47	ANOVA across all 4 groups: p:0.105
McKenney, 2007[36]	SMV20mg +EZE10mg	Continuous LDLc mg/dl calculated	72	Mean: 202 SD: 44	8 weeks	NR	NR	% Change from baseline: -53 95% CI: -56,-50	NR
Robinson, 2009[43]	ATV 20mg	LDLc	215	Mean: 139, SD: 33	6 weeks	215	Mean: 120.0,	%change from baseline:-39.4	NR
Robinson,	ATV 40mg	LDLc	217	Mean: 140,	6 weeks	217	Mean: 119.0,	%change from	NR

Author, Year	Arm	Outcome Units	Baseline N	Baseline Outcome	Timepoint (s)	N at Timepoint (s)	Outcomes at Timepoint(s)	Within Arm Comparisons	Between Arm Comparison
2009[43]				SD: 33				baseline:-46.0,	
Robinson, 2009[43]	SMV20mg +EZE10mg	LDLc	219	Mean: 137, SD: 33	6 weeks	219	Mean: 120.0, ,	%change from baseline:-49.6,	NR
Stein, E, 2004[46]	ATV 20mg	Continuous LDL c direct mg/dl	316	Arm 1: Mean: 187.3 SE: 2.6	4 weeks	303	NR	Absolute change: -16.1 Mean % change: -8.6 SE: 0.7	Btw group % change: -14.2, p<0.01 monotherapy vs. combination
Stein, E, 2004[46]	ATV 20mg +EZE10mg	Continuous LDLc direct mg/dl	305	Arm 2: Mean: 186.2 SE: 2.7	4 weeks	293	NR	Absolute change: -42.6 Mean % change: -22.8 SE: 0.7	NR
Zieve, 2010[48] Ben-Yehida, 2011[49]	ATV 20mg/40mg	LDLc mg/dl , Measured	527	Mean: 102, SD: 21	12 weeks	509	NR	LCL 95%: -21 , HCL 95%: -15 , Least squares mean % change:-18	NR
Zieve, 2010[48] Ben-Yehida, 2011[49]	ATV10mg +EZE10mg	LDLc mg/dl , Measured	526	Mean: 103, SD: 28	12 weeks	516	NR	LCL 95%:-25, HCL 95%: -20, Least squares mean % change:-23	p: 0.001, 95%LCL:-7, 95%HCL:-2, Least Squares Mean% Change: -5, comparing monotherapy vs. combination at 12 weeks
***Low* potency statin combination therapy versus *mid* potency statin monotherapy**									

Author, Year	Arm	Outcome Units	Baseline N	Baseline Outcome	Timepoint (s)	N at Timepoint (s)	Outcomes at Timepoint(s)	Within Arm Comparisons	Between Arm Comparison
Ballantyne, 2004[12]	ATV 10mg	Continuous LDLc mg/dl	235	Mean: 175.3 SD: 36.4	6 weeks	235	NR	% Change from baseline: -36.1	NR
Ballantyne, 2004[12]	SMV 10mg +EZE10mg	Continuous LDLc mg/dl	230	Mean: 176.7 SD: 33.0	6 weeks	230	NR	% Change from baseline: -47.1	p<0.001, vs. ATV 10
Bays, 2004[50]	SMV 20mg	Continuous LDLc mg/dl calculated	NR	NR	12 weeks	144-147	NR	Least squares mean percent change in efficacy parameters from baseline to 12 weeks: -34.2	NR
Bays, 2004[50]	SMV 10mg +EZE10mg	Continuous LDLc mg/dl calculated	NR	NR	12 weeks	140-151	NR	-44.8	NR
Davidson, 2002[18]	SMV 20mg	Continuous LDLc measured mg/dl	61	NR	12 weeks	53	NR	Mean% change from baseline: -36	NR
Davidson, 2002[18]	SMV 10 +EZE10mg	NR	67	NR	12 weeks	61	NR	Mean% change from baseline: -44	NR
Feldman, 2004[19]	SMV 20mg	LDLc mg/dl	253	Mean:173.8 SD:44.7	5 weeks	246	NR	Least squares %change from baseline(SE): -38(0.8)	NR
Feldman, 2004[19]	SMV10mg +EZE10mg	LDLc mg/dl	251	Mean:165.1 SD:34.3	5 weeks	242	NR	Least squares %change from baseline(SE): -47(0.8)	p<0.001 monotherapy vs. combination
Goldberg, 2004[23]	SMV 40mg	Continuous LDLc	NR	NR	12 weeks	90	NR	Mean% change from baseline: -	NR

Author, Year	Arm	Outcome Units	Baseline N	Baseline Outcome	Timepoint (s)	N at Timepoint (s)	Outcomes at Timepoint(s)	Within Arm Comparisons	Between Arm Comparison
		mg/dl calculated						41.5 IQR: -40, -50	
Goldberg, 2004[23]	SMV 80mg	Continuous LDLc mg/dl calculated	NR	NR	12 weeks	87	NR	Mean% change from baseline: -45.6 IQR: -41.5, -57	NR
Goldberg, 2004[23]	SMV10mg +EZE10mg	Continuous LDLc mg/dl calculated	NR	NR	12 weeks	87	NR	Mean% change from baseline: -46.2 IQR: -42,-57	p<0.001 monotherapy vs. combination
Her, 2013 [28]	ATV/EZE 5/5 mg	Mg/dL	26	Mean: 165 SD:20	8 weeks	26	Mean:81 SD:14	% change= -50 SD= 8 P<0.001	P=0.22 (ANOVA)
Her, 2013 [28]	RSV10 mg	Mg/dL	25	Mean:163 SD:21	8 weeks	25	Mean:81 SD:21	% change= -50 SD= 13 P<0.001	
Kerzner, 2003[30]	LOV 40mg	Continuous LDLc mg/dl measured	NR	NR	12 weeks	NR	NR	Mean percentage change from baseline: -29	NR
Kerzner, 2003[30]	LOV 20mg +EZE10mg	Continuous LDLc mg/dl measured	NR	NR	12 weeks	NR	NR	Mean percentage change from baseline: -39	NR
Kerzner, 2003[30]	LOV 10mg +EZE10mg	LDLc measured	NR	NR	12 weeks	NR	NR	Mean percentage change from baseline: -33	NR

\ATV atorvastatin; EZE Ezetimibe; HCL higher confidence limit; IQR interquartile range; LCL lower confidence limit; LDLc low density lipoprotein cholesterol; LOV Lovastatin; NR not reported; NS Not significant; RSV Rosuvastatin; SD standard deviation; SE standard error; SMV simvastatin

Evidence Table E15. HDL-c – general population

Author, Year	Arm	Outcome Units	Baseline N	Baseline Outcome	Timepoint (s)	N at Timepoint(s)	Outcomes at Timepoint(s)	Within Arm Comparisons	Between Arm Comparisons
***Low* potency statin combination therapy versus *high* potency statin monotherapy**									
Araujo, 2010[9]	SMV	HDLc	12	SD: 7.66, Counts:44.65	4weeks	12	SD: 8.29, Mean: 42.39	% Change: -5.06, p:0.037, 4 weeks vs. 0 weeks	NR
Araujo, 2010[9]	SMV +EZE	HDLc	11	SD: 7.92, Counts:45.08	4 weeks	11	SD: 8.44 Mean: 45.13,	%Change: 0.08, p:0.976, 4 weeks vs. 0 weeks,	NR
Ballantyne, 2005[12]	ATV 20mg	Continuous HDLc mg/dl	230	Mean: 48.7 SD: 11.7	6 weeks	230	NR	% Change from baseline: 5.1	NR
Ballantyne, 2005[12]	ATV 40mg	Continuous HDLc mg/dl	232	Mean: 50.2 SD: 13.1	6 weeks	232	NR	% Change from baseline: 3.8	NR
Ballantyne, 2005[12]	ATV 80mg	Continuous HDLc mg/dl	230	Mean: 48.0 SD: 10.2	6 weeks	230	NR	% Change from baseline:1.4	NR
Ballantyne, 2005[12]	SMV 10mg +EZE 10mg	Continuous HDLc mg/dl	230	Mean: 49.2 SD: 12.1	6 weeks	230	NR	% Change from baseline: 7.7	NR
Bays, 2004[50]	SMV 40mg	Continuous HDLc mg/dl	NR	NR	12 weeks	150-154	NR	Least squares mean % change in efficacy parameters from baseline to 12 weeks: 7.5	NR

Bays, 2004[50]	SMV 80mg	Continuous HDLc mg/dl	NR	NR	12 weeks	150-156	NR	Least squares mean % change in efficacy parameters from baseline to 12 weeks: 7.1	NR
Bays, 2004[50]	SMV 10mg +EZE10mg	Continuous HDLc mg/dl	NR	NR	12 weeks	140-151	NR	Least squares mean % change in efficacy parameters from baseline to 12 weeks: 8.0	NR
Davidson, 2002[18]	SMV 40mg	Continuous HDLc mg/dl	65	NR	12 weeks	60	NR	Mean% change from baseline: 6 p:0.02	NR
Davidson, 2002[18]	SMV 80mg	Continuous HDLc mg/dl	67	NR	12 weeks	63	NR	Mean% change from baseline: 8 p:0.93	NR
Davidson, 2002[18]	SMV10mg +EZE 10mg	Continuous HDLc mg/dl	67	NR	12 weeks	61	NR	Mean% change from baseline: 9 p:ns	NR
Florentin, 2011[20]	SMV 40mg	HDLc , mg/dl	50	Mean: 60, SD: 13,	3months	50	Mean: 60, SD: 13, ,	% change from baseline: 0.3, pvalue:ns	NR
Florentin, 2011[20]	SMV 10mg +EZE10mg	HDLc , mg/dl	50	Mean: 59, SD: 14,	3months	50	Mean: 59, SD: 14, ,	% change from baseline:0.3, p:ns	NR
Her, 2013 [28]	ATV 20 mg	Mg/dL	25	Mean:50.4 SD:9.1	8 weeks	25	Mean:51.3 SD:13.2	% change= 1.7 SD= 16.8 P=0.48	P=0.78 (ANOVA)
Her, 2013 [28]	ATV/EZE 5/5 mg	Mg/dL	26	Mean: 49.3 SD:9.3	8 weeks	26	Mean:51.2 SD:9.0	% change=4.6 SD= 11 P=0.09	NR
Lee, 2011[31]	ATV 20mg	HDLc	30	Mean: 50.5, SD: 8.8,	8weeks	30	Mean: 49.7, SD: 7.8, ,	% change from baseline: -1 ± 10, pvalue:0.46	NR
Lee, 2011[31]	ATV 5mg +EZE 5mg	HDLc	30	Mean: 49.7, SD: 7.8,	8weeks	30	Mean: 53.6, SD: 12, ,	% change from baseline:4 ± 10, pvalue:0.02	p: 0.08 vs. ATV 20

Lee, 2012[32]	ATV 20	HDLc	28	Mean: 47.6, SD: 7.7	8weeks	28	Mean: 49.0, SD: 7.5	Net mean diff:1.4, % change from baseline:3% (calculated), SD: 4.9, p:0.15	NR
Lee, 2012[32]	ATV 5mg +EZE 5mg	HDLc	32	Mean: 45.7, SD: 8.4	8weeeks	32	Mean: 49.3, SD: 9.5,	Net mean diff.: 3.6, % change from baseline:9% (calculated), SD:6.7, P:0.01	p: 0.09 , vs. ATV 20
Liberopoulos, 2013[34]	SMV 40mg	HDLc mg/dl measured	25	Mean: 62, SD: 12	3 months	25	Mean: 64, SD: 12	Mean diff. from baseline:1.6, p:ns	NR
Liberopoulos, 2013[34]	SMV 10mg +EZE 10mg	HDLc	25	Mean: 59, SD: 11	3 months	25	Mean: 60, SD: 11	Mean diff. from baseline:1.6, p:ns	NR
Moutzouri, 2011[37]	SMV 40 mg	HDLc mg/dl	55	Mean: 58, SD: 13	12 weeks	55	Mean: 59, SD: 14	p= ns 0 weeks vs. 12 weeks	NR
Moutzouri, 2011[37]	RSV 10mg	HDLc mg/dl	45	Mean: 61 SD: 13	12 weeks	45	Mean: 63 SD: 14	p= ns 0 weeks vs. 12 weeks	NR
Moutzouri, 2011[37]	SMV 10mg +EZE 10 mg	HDLc mg/dl	53	Mean: 60, SD: 12	12 weeks	53	Mean: 61, SD: 12	p= ns 0 weeks vs. 12 weeks	NR
Moutzouri, 2012[38]	SMV 80mg	HDLc mg/dl	30	Mean: 60, SD: 12	12 weeks	30	Mean: 60, SD: 11	NR	NR
Moutzouri, 2012[38]	SMV 10mg +EZE 10mg	HDLc mg/dl	30	Mean: 61, SD: 14	12 weeks	30	Mean: 59, SD: 11	NR	p=ns vs.SMV 80
***Mid* potency statin combination therapy versus *high* potency statin monotherapy**									
Ballantyne 2003[11]	ATV 20mg	Continuous HDLc measured	NR	NR	12 weeks	NR	NR	% mean change from baseline:4	NR
Ballantyne, 2003[11]	ATV 40mg	Continuous HDLc measured	NR	NR	12 weeks	NR	NR	% mean change from baseline: 4	NR

Ballantyne, 2003[11]	ATV 80mg	Continuous HDLc measured	NR	NR	12 weeks	NR	NR	% mean change from baseline: 3	NR
Ballantyne, 2003[11]	ATV 10mg +EZE 10mg	Continuous HDLc measured	NR	NR	12 weeks	NR	NR	% mean change from baseline: 9	NR
Ballantyne, 2005[12]	ATV 20mg	Continuous HDLc mg/dl	230	Mean: 48.7 SD: 11.7	6 weeks	230	NR	% Change from baseline: 5.1	NR
Ballantyne, 2005[12]	ATV 40mg	Continuous HDLc mg/dl	232	Mean: 50.2 SD: 13.1	6 weeks	232	NR	% Change from baseline: 3.8	NR
Ballantyne, 2005[12]	ATV 80mg	Continuous HDLc mg/dl	230	Mean: 48.0 SD: 10.2	6 weeks	230	NR	% Change from baseline:1.4	NR
Ballantyne, 2005[12]	SMV 20mg +EZE 10mg	Continuous HDLc mg/dl	233	Mean: 49.1 SD: 13.2	6 weeks	233	NR	% Change from baseline: 7.2	NR
Bays, 2004[50]	SMV 40mg	Continuous HDLc mg/dl	NR	NR	12 weeks	150-154	NR	Least squares mean % change in efficacy parameters from baseline to 12 weeks: 7.5	NR
Bays, 2004[50]	SMV 80mg	Continuous HDLc mg/dl	NR	NR	12 weeks	150-156	NR	Least squares mean % change in efficacy parameters from baseline to 12 weeks: 7.1	NR
Bays, 2004[50]	SMV 20mg + EZE10mg	Continuous HDLc mg/dl	NR	NR	12 weeks	140-153	NR	Least squares mean % change in efficacy parameters from baseline to 12 weeks: 9.8	NR

Catapano, 2006[15]	RSV 10mg	HDLc mg/dl	475	Mean:51	6 weeks	478	NR	Least squares mean %change from baseline(SE): 6.7(0.5)	NR
Catapano, 2006[15]	RSV 20mg	HDLc mg/dl	478	Mean:50	6 weeks	478	NR	Least squares mean %change from baseline(SE): 8.1(0.5)	NR
Catapano, 2006[15]	RSV 40mg	HDLc mg/dl	475	Mean:50	6 weeks	475	NR	Least squares mean % change from baseline(SE): 8.1(0.5)	NR
Catapano, 2006[15]	SMV20mg +EZE 10mg	HDLc mg/dl	476	Mean:51	6 weeks	476	NR	Least squares mean % change from baseline(SE): 7.0(0.5)	NR
Davidson, 2002[18]	SMV 40mg	Continuous HDLc measured	65	NR	12 weeks	60	NR	Mean% change from baseline: 6 p:0.02	NR
Davidson, 2002[18]	SMV 80mg	Continuous HDLc measured	67	NR	12 weeks	63	NR	Mean% change from baseline: 8 p:0.93	NR
Davidson, 2002[18]	SMV 20mg +EZE10mg	Continuous HDLc measured	69	NR	12 weeks	58	NR	Mean% change from baseline: 9 p:ns	NR
Foody, 2010[21]	ATV 20mg	HDLc	248-257	Mean: 54, SD: 14	12 weeks	238	NR	% change from baseline:3.8 12 weeks vs. 0 weeks	NR
Foody, 2010[21]	ATV 40mg	HDLc	245-256	Mean: 53, SD: 13	12 weeks	239	NR	% change from baseline:5.2 12 weeks vs. 0 weeks	NR
Foody, 2010[21]	SMV 20mg +EZE 10mg	HDLc	253-258	Mean: 54, SD: 14	12 weeks	232	NR	% change from baseline:7.0 12 weeks vs. 0 weeks	p: <0.05, N Analyzed: 470, Diff.Least squares Mean:-3.3 Vs. ATV 20

McKenny, 2007[36]	RSV 20 mg	Continuous HDLc mg/dl measured	73	Arm 2: Mean: SD:	8 weeks	NR	NR	% Change from baseline: +7 95% CI: +4, +10	ANOVA across all 4 groups: p<0.001
McKenney, 2007[36]	SMV 20mg +EZE 10mg	Continuous HDLc mg/dl measured	72	Arm 2: Mean: SD:	8 weeks	NR	NR	% Change from baseline: +8 95% CI: +5, +11	NR
Robinson, 2009[43]	ATV 20mg	HDLc	215	Mean: 44, SD: 10	6weeks	215	%change from base: 5.6	NR	NR
Robinson, 2009[43]	ATV 40mg	HDLc	217	Mean: 42, SD: 11	6weeks	217	%change from base: 4.9	NR	p: <0.05 , Treatment Diff: 3.4, Vs. ATV 20
Robinson, 2009[43]	SMV 20mg +EZE 10mg	HDLc	219	Mean: 44, SD: 11	6 weeks	219	%change from base: 6.8	NR	NR
Stein, 2004[46]	ATV 20mg	Continuous HDLc mg/dl	316	Arm 1: Mean: 49.9, SE: 0.7	4 weeks	303	NR	Absolute change: 0.4 Mean % change: 1.3 SE: 0.6	Btw group % change: 0.9 p=ns monotherapy vs. combination
Stein, 2004[46]	ATV 10mg +EZE10mg	Continuous HDLc mg/dl	305	Arm 2: Mean: 50.0, SE: 0.7	4 weeks	293	NR	Absolute change: 0.8 Mean % change: 2.1 SE: 0.6	NR
Zieve, 2010[48] Ben-Yehida, 2011[49]	ATV 20mg/40mg	HDLc mg/dl Calculated	527	Mean:54, SD:12	12 weeks	509	NR	LCL 95%: -2 , HCL 95%: 1, Least squares mean % change: -1, 12 weeks vs. 0 weeks	NR

Zieve, 2010[48] Ben-Yehida, 2011[49]	ATV 10mg + EZE10mg	HDLc mg/dl Calculated	526	Mean:55, SD:14	12 weeks	516	NR	LCL 95%: 1 , HCL 95%: 4 Least squares mean %change: 2, 6 weeks vs. 0 weeks	pvalue:< 0.001 , 95%LCI:2 95%HCL:5, Least squares Mean % Change:3 2, Vs. ATV 20/40
***Low* potency statin combination therapy versus *mid* potency statin monotherapy**									
Ballantyne, 2004[12]	ATV 10mg	Continuous HDLc mg/dl	235	Mean: 48.2 SD: 12.5	6 weeks	235	NR	% Change from baseline: 6.9	NR
Ballantyne, 2005[12]	SMV 10mg +EZE 10mg	Continuous HDLc mg/dl	230	Mean: 49.2 SD: 12.1	6 weeks	230	NR	% Change from baseline: 7.7	NR
Bays, 2004[50]	SMV 20mg	Continuous HDLc mg/dl	NR	NR	12 weeks	144-147	NR	Least squares mean % change in efficacy parameters from baseline to 12 weeks: 7.4	NR
Bays, 2004[50]	SMV 10mg +EZE10mg	Continuous HDLc mg/dl	NR	NR	12 weeks	140-151	NR	Least squares mean % change in efficacy parameters from baseline to 12 weeks: 8.0	NR
Davidson, 2002[18]	SMV 20mg	Continuous HDLc mg/dL measured	61	NR	12 weeks	53	NR	Mean% change from baseline: 6 p:0.10	NR
Davidson, 2002[18]	SMV10mg +EZE 10mg	NR	67	NR	12 weeks	61	NR	Mean% change from baseline: 9 p:ns	NR
Feldman, 2004[19]	SMV 20mg	HDLc mg/dl	253	Mean:46.1 SD:11.2	5 weeks	248	NR	Least squares mean %change from baseline(SE): 5.1(0.7)	NR

Feldman, 2004[19]	SMV 10mg +EZE 10mg	HDLc mg/dl	251	Mean:44.6, SD:10.2	5 weeks	245	NR	Least squares mean %change from baseline(SE): 6.2(0.7)	NR
Her, 2013 [28]	RSV 10 mg	HDLc mg/dl	25	Mean:50.3 SD:10.3	8 weeks	25	Mean:51.7 SD:11.5	% change= 3.6 SD= 16.6 P=0.42	NR
Her, 2013 [28]	ATV/EZE 5/5 mg	HDLc mg/dl	26	Mean: 49.3 SD:9.3	8 weeks	26	Mean:51.2 SD:9.0	% change=4.6 SD= 11 P=0.09	NR
Kerzner, 2003[30]	LOV 40mg	Continuous HDLc mg/dL measured	NR	NR	12 weeks	NR	NR	Mean % change from baseline: 5	NR
Kerzner, 2003[30]	LOV 20mg EZE 10mg	Continuous	NR	NR	12 weeks	NR	NR	Mean % change from baseline: 9	NR
Kerzner, 2003[30]	LOV 10mg EZE10mg	HDLc measured	NR	NR	12 weeks	NR	NR	Mean% change from baseline: 8	NR

ATV atorvastatin; EZE Ezetimibe; HCL higher confidence limit; HDLc high density lipoprotein cholesterol; IQR interquartile range; LCL lower confidence limit; LOV Lovastatin; NR not reported; NS Not significant; RSV Rosuvastatin; SD standard deviation; SE standard error; SMV simvastatin

Evidence Table E16. Total cholesterol:HDL – general population

Author, Year	Arm	Outcome Units	Baseline N	Baseline Outcome	Timepoint (s)	N at Timepoint(s)	Outcomes at Timepoint(s)	Within Arm Comparisons	Between Arm Comparisons
***Low* potency statin combination therapy versus *high* potency statin monotherapy**									
Bays, 2004[50]	SMV 40mg	TC: HDLc	NR	NR	12 weeks	150-154	NR	-33.2	
Bays, 2004[50]	SMV 80mg	TC: HDLc	NR	NR	12 weeks	150-156	NR	-38.4	NR
Bays, 2004[50]	SMV 10mg +EZE10mg	TC: HDLc	NR	NR	12 weeks	140-151	NR	-35.8	p< 0.001, vs. SMV 40
***Mid* potency statin combination therapy versus *high* potency statin monotherapy**									
Ballantyne, 2003[11]	ATV 20mg	TC:HDLc	NR	NR	12 weeks	NR	NR	% mean change from baseline: -32	NR
Ballantyne, 2003[11]	ATV 40mg	TC:HDLc	NR	NR	12 weeks	NR	NR	% mean change from baseline:-34	NR
Ballantyne, 2003[11]	ATV 80mg	TC:HDLc	NR	NR	12 weeks	NR	NR	% mean change from baseline: -41	NR
Ballantyne, 2003[11]	ATV 10mg +EZE 10mg	TC:HDLc	NR	NR	12 weeks	NR	NR	% mean change from baseline:-43	NR
Catapano, 2006[15]	RSV 10mg	TC:HDL	478	Mean:5.4	6 weeks	478	NR	Least Squares mean % change from baseline (SE): -36.1(0.5)	NR
Catapano, 2006[15]	RSV 20mg	TC:HDL	478	Mean:5.4	6 weeks	478	NR	Least Squares mean % change from baseline (SE): -41.4(0.5)	NR
Catapano, 2006[15]	RSV 40mg	TC:HDLc	475	Mean:5.4	6 weeks	475	NR	Least Squares mean % change from baseline (SE): -44.5(0.5)	NR

Catapano, 2006[15]	SMV 20mg +EZE 10mg	TC:HDLc	476	Mean:5.3	6 weeks	476	NR	Least Squares mean % change from baseline(SE): -40.3(0.5)	NR
Foody, 2010[21]	ATV 20mg	TC:HDLc ratio	248-257	Mean: 4.9, SD: 1.2	12 weeks	238	NR	% change from baseline to 12 weeks:-35.0	NR
Foody, 2010[21]	ATV 40mg	TC:HDLc	245-256	Mean: 5.1, SD: 1.3	12 weeks	239	NR	% change from baseline to 12 weeks:-37.6	NR
Foody, 2010[21]	SMV 20mg +EZE 10mg	TC:HDLc	253-258	Mean: 4.9, SD: 1.1	12 weeks	232	NR	% change from baseline to 12 weeks:-41.1	p: <0.001 , Diff. Least Squares Mean: -6.2, comparing vs. ATV 20
McKenny, 2007[36]	RSV 20 mg	TC: HDLc	73	NR	8 weeks	NR	NR	% Change from baseline: -40 95% CI: -43, -38	ANOVA across all 4 groups: p:0.027
McKenny, 2007[36]	SMV 20mg +EZE 10mg	TC: HDLc	72	NR	8 weeks	NR	NR	% Change from baseline: -43 95% CI: -46, -41	NR
Robinson, 2009[43]	ATV 20mg	TC:HDLc	215	Mean: 5, SD: 1	6 weeks	215	%change from base: -31.5,	NR	NR
Robinson, 2009[43]	ATV 40mg	TC:HDLc	217	Mean: 6, SD: 1	6 weeks	217	%change from base: -35.3,	NR	NR
Robinson, 2009[43]	SMV 20 +EZE 20mg	TC:HDLc	219	Mean: 5, SD: 1	6 weeks	219	%change from base: -36.9,	NR	p: <0.001 , Treatment Diff: -8.8, comparing ATV 40

Stein, 2004[46]	ATV 20mg	Continuous Tc:HDLc	316	Mean: 5.6, SE: 0.09	4 weeks	303	NR	Absolute change: -0.4 Mean % change: -6.8 SE: 0.6	Btw group % change: -11.8 p<0.01,
Stein, 2004[46]	ATV 10mg +EZE 10mg	Continuous Tc:HDLc	305	Mean: 5.52, SE: 0.09	4 weeks	293	NR	Absolute change: -1.1 Mean % change: -18.6 SE: 0.7	NR
Zieve, 2010[48] Ben-Yehida, 2011[49]	ATV 20/40 mg	TC:HDLc	527	Mean:4, SD:1	12 weeks	509	NR	LCL 95%: -12 , HCL 95%: -8 , Least Squares mean % change: -10	NR
Zieve, 2010[48] Ben-Yehida, 2011[49]	ATV10mg + EZE 10mg	TC:HDLc	526	Mean:4, SD:1	12 weeks	516	NR	LCL 95%: -16 , HCL 95%: -13 , Least Squares mean % change: -14	pvalue:<0.001, 95%LCI:-7, 95%HCI:-2, Least Squares Mean% Change: -5 comparing ATV 20/40

ATV atorvastatin; EZE Ezetimibe; HCL higher confidence limit; HDLc high density lipoprotein cholesterol; IQR interquartile range; LCL lower confidence limit; LOV Lovastatin; NR not reported; NS Not significant; RSV Rosuvastatin; SD standard deviation; SE standard error; SMV simvastatin; TC Total cholesterol

Evidence Table E17. Adherence – general population

Author, Year	Arm	Outcome Units	Baseline N	Baseline Outcome	Timepoint (s)	N at Timepoint(s)	Outcomes at Timepoint(s)	Within Arm Comparisons	Between Arm Comparisons
<u>Mid</u> potency statin combination therapy versus <u>high</u> potency statin monotherapy									
McKenny, 2007[36]	RSV 20 mg	Adherence to treatment (defined as returning between 75 and 125% of tablets dispensed)	73	NR	8 weeks	NR	%= 84	NR	NR
McKenny, 2007[36]	SMV/EZE (20/10)	Adherence to treatment (defined as returning between 75 and 125% of tablets dispensed)	72	NR	8 weeks	NR	%= 99	NR	NR
<u>Mid</u> potency statin combination therapy versus <u>high</u> potency statin monotherapy									
Foody, 2010[21]	ATV 20mg	At least one adverse event	259	NR	12 weeks	258	N(%) with events: 60(23.3),	NR	NR
Foody, 2010[21]	ATV 40mg	At least one adverse event	257	NR	12 weeks	256	N(%) with events: 67(26.2)	NR	NR
Foody, 2010[21]	SMV 20 +EZE10mg	At least one adverse event	259	NR	12 weeks	256	N(%) with events: 71(27.7)	NR	NR
Stein, 2004[46]	ATV 20mg	At least one adverse event	316	NR	12 weeks	316	N(%)with events:184(58)	NR	NR

Stein, 2004[46]	ATV 10mg +EZE 10mg	At least one adverse event	305	NR	12 weeks	305	N(%)with events:193(63)	NR	NR
Zieve, 2010[48] Ben-Yehida, 2011[49]	ATV 20/40mg	At least one adverse event,	527	NR	12 weeks	525	N(%) with events: 159(30)	NR	NR
Zieve, 2010[48] Ben-Yehida, 2011[49]	ATV 10mg + EZE10mg	At least one adverse event	526	NR	12 weeks	526	N(%) with events :143(27)	NR	NR
***Low** potency statin combination therapy versus **mid** potency statin monotherapy*									
Feldman, 2004[19]	SMV 20mg	An adverse event	253	NR	23 weeks	253	N(%)with events:168(66)	NR	NR
Feldman, 2004[19]	SMV 10mg +EZE 10mg	An adverse event	251	NR	23 weeks	251	N(%)with events:140(56)	NR	NR

ATV Atorvastatin; EZE Ezetimibe; NR not reported; RSV Rosuvastatin; SMV simvastatin;

Evidence Table E18. Withdrawal due to adverse events – general population

Author, Year	Arm	Outcome Units	Baseline N	Baseline Outcome	Timepoint (s)	N at Timepoint(s)	Outcomes at Timepoint(s)	Within Arm Comparisons	Between Arm Compariso ns
***Low** potency statin combination therapy versus **high** potency statin monotherapy*									
Davidson, 2002[18]	SMV 40	Withdrawal due to adverse events	65	N/A	12 weeks	65	N=2 Percent: 3.1	NR	NR
Davidson, 2002[18]	SMV 80	Withdrawal due to adverse events	67	N/A	12 weeks	67	N=2 Percent: 3.0	NR	NR
Davidson, 2002[18]	EZE/SMV (10/10)	Withdrawal due to adverse events	67	N/A	12 weeks	67	N=2 Percent: 3.0	NR	NR

Her, 2013 [28]	ATV 20 mg	Withdrawal due to adverse events	25	N/A	8 weeks	25	1 (4)	NR	NR
Her, 2013 [28]	ATV/EZE 5/5 mg	Withdrawal due to adverse events	26	N/A	8 weeks	26	0(0)	NR	NR
<u>Mid</u> potency statin combination therapy versus <u>high</u> potency statin monotherapy									
Davidson, 2002 [18]	SMV 40 mg	Withdrawal due to adverse events	65	N/A	12 weeks	65	N=2 Percent: 3.1	NR	NR
Davidson, 2002 [18]	SMV 80 mg	Withdrawal due to adverse events	67	N/A	12 weeks	67	N: 2 Percent: 3.0	NR	NR
Davidson, 2002 [18]	EZE/SMV (10/20) mg	Withdrawal due to adverse events	69	N/A	12 weeks	69	N=7 Percent: 1.0	NR	NR
Foody, 2010 [21]	ATV 20mg	Withdrawal due to adverse events ,	258	N/A	12 weeks	258	N with events: 3, %with events: 1.2 ,	NR	NR
Foody, 2010 [21]	ATV 40mg	Withdrawal due to adverse events ,:	256	N/A	12 weeks	256	N with events: 5, %with events: 2 ,	NR	NR
Foody, 2010 [21]	SMV 20mg +EZE 10mg	Withdrawal due to adverse events ,	256	N/A	12 weeks	256	N with events: 9, %with events: 3.5 ,	NR	NR
Zieve, 2010[48] Ben-Yehida, 2011[49]	ATV 20/40mg	Withdrawal due to adverse events ,	527	N/A	12 weeks	525	%: 2, N with events: 8 ,	NR	NR
Zieve, 2010[48] Ben-Yehida, 2011[49]	ATV 10mg + EZE 10mg	Withdrawal due to adverse events ,	526	N/A	12 weeks	526	%: 3, N with events: 14 ,	NR	NR
<u>Low</u> potency statin combination therapy versus <u>mid</u> potency statin monotherapy									

Davidson, 2002 [18]	SMV 20 mg	Withdrawal due to adverse events	61	N/A	12 weeks	61	N=6 Percent: 9.8	NR	NR
Davidson, 2002 [18]	EZE/SMV (10/10) mg	Withdrawal due to adverse events	67	N/A	12 weeks	67	N=2 Percent: 3.0	NR	NR
Feldman, 2004 [19]	SMV 20mg	Withdrawing from trial due to adverse event	253	N/A	23 weeks	253	N(%):14(5.5)	NR	NR
Feldman, 2004 [19]	SMV 10mg +EZE 10mg	Withdrawing from trial due to adverse event	251	N/A	23 weeks	251	N(%):11(4.4)	NR	NR

ATV Atorvastatin; EZE Ezetimibe; N/A Not applicable; NR not reported; SMV simvastatin

Evidence Table E19. Elevated liver transaminases – general population

Author, Year	Arm	Outcome Units	Baseline N	Baseline Outcome	Timepoint (s)	N at Timepoint(s)	Outcomes at Timepoint(s)	Within Arm Comparisons	Between Arm Comparisons
<u>Low</u> potency statin combination therapy versus <u>high</u> potency statin monotherapy									
Her, 2013 [28]	ATV 20 mg	Events	25	N/A	8 weeks	25	0(0)	NR	NR
Her, 2013 [28]	ATV/EZE 5/5 mg	Events	26	N/A	8 weeks	26	0(0)	NR	NR
Lee, 2011 [31]	ATV 20mg	Elevated AST and/or ALT > 3x ULN and/or hepatitis	30	NR	8 weeks	30	N with events: 0	NR	NR
Lee, 2011 [31]	ATV 5mg +EZE 5mg	Elevated AST and/or ALT > 3x ULN and/or hepatitis	30	NR	8 weeks	30	N with events: 0	NR	NR

Lee, 2012[32]	ATV 20	Elevated AST and/or ALT > 3x ULN and/or hepatitis	28	NR	8 weeks	28	N with events: 0	NR	NR
Lee, 2012[32]	ATV 5mg +EZE 5mg	Elevated AST and/or ALT > 3x ULN and/or hepatitis	32	NR	8 weeks	32	N with events: 0	NR	NR
<u>Mid</u> potency statin combination therapy versus <u>high</u> potency statin monotherapy									
Catapano, 2006[15]	RSV 20mg	Elevated AST and/or ALT ≥ 3xULN and/or hepatitis	492	NR	NR	NR	N with event:0	NR	NR
Catapano, 2006[15]	RSV 20mg	Elevated AST and/or ALT ≥ 3xULN and/or hepatitis	495	NR	NR	NR	N with event:2	NR	NR
Catapano, 2006[15]	RSV 40mg	Elevated AST and/or ALT ≥ 3x ULN and/or hepatitis	494	NR	NR	NR	N with event:1	NR	NR
Catapano, 2006[15]	SMV 20mg +EZE 10mg	Elevated AST and/or ALT ≥ 3x ULN and/or hepatitis	492	NR	NR	NR	N with event:1	NR	NR
Foody, 2010[21]	ATV 20mg	Elevated AST and/or ALT > 3x ULN and/or hepatitis	259	NR	12 weeks	246	N(%)with events:0(0)	NR	NR

Foody, 2010[21]	ATV 40mg	Elevated AST and/or ALT > 3x ULN and/or hepatitis,	257	NR	12 weeks	248	N(%)with events:3(1.2)	NR	NR
Foody, 2010[21]	SMV 20mg +EZE 10mg	Elevated AST and/or ALT > 3x ULN and/or hepatitis	259	NR	12 weeks	250	N(%)with events:2(0.8)	NR	NR
McKenny, 2007[36]	RSV 20 mg	Elevated AST/ALT >3x ULN	73	NR	12 weeks	NR	N with event:1	NR	NR
McKenny, 2007[36]	SMV 20mg +EZE 10mg	Elevated AST/ALT >3x ULN	72	NR	12 weeks	NR	N with event: 0	NR	NR
Robinson, 2009[43]	ATV 20mg	Elevated AST and/or ALT > 3x ULN and/or hepatitis	NR	NR	6 weeks	220	N(%)with events:0(0)	NR	NR
Robinson, 2009[43]	ATV 40mg	Elevated AST and/or ALT > 3x ULN and/or hepatitis	NR	NR	6 weeks	218	N(%)with events:2(0.9)	NR	NR
Robinson, 2009[43]	SMV 20 +EZE 10mg	Elevated AST and/or ALT > 3x ULN and/or hepatitis	NR	NR	6 weeks	223	N(%)with events:4(1.8)	NR	NR
Stein, 2004[46]	ATV 20mg	Elevated ALT and/or AST≥ 3x ULN	316	NR	12 weeks	316	N(%)with event:1(<1)	NR	NR
Stein, 2004[46]	ATV10mg +EZE10mg	ALT and/or AST≥ 3x ULN	305	NR	12 weeks	305	N(%)with event:3(1)	NR	NR

Zieve, 2010[48] Ben-Yehida, 2011[49]	ATV 20/40 mg	Elevated AST and/or ALT > 3x ULN and/or hepatitis	527	NR	12 weeks	520	N(%)with events:2(1)	NR	NR
Zieve, 2010[48] Ben-Yehida, 2011[49]	ATV 10mg + EZE 10mg	Elevated AST and/or ALT > 3x ULN and/or hepatitis	526	NR	12 weeks	520	N(%)with events:2(<1)	NR	NR
***Low* potency statin combination therapy versus *mid* potency statin monotherapy**									
Feldman, 2004[19]	SMV 20mg	Elevated AST and/or ALT ≥ 3x ULN and/or hepatitis	248	NR	23 weeks	248	N(%)with event:0(0)	NR	NR
Feldman, 2004[19]	SMV 10mg +EZE10mg	Elevated AST and/or ALT ≥ 3x ULN and/or hepatitis	245	NR	23 weeks	245	N(%)with event:1(0.4)	NR	NR
Her, 2013 [28]	RSV 10 mg	Events	25	N/A	8 weeks	25	0(0)	NR	NR
Her, 2013 [28]	ATV/EZE 5/5 mg	Events	26	N/A	8 weeks	26	0(0)	NR	NR

ALT Alanine transaminase; AST Aspartate transaminase; ATV Atorvastatin; EZE Ezetimibe; N/A Not applicable; NR not reported; RSV Rosuvastatin; SMV simvastatin; ULN Upper normal limit

Evidence Table E20. Musculoskeletal adverse events – general population

Author, Year	Arm	Outcome Units	Baseline N	Baseline Outcome	Timepoint (s)	N at Timepoint(s)	Outcomes at Timepoint(s)	Within Arm Comparisons	Between Arm Comparisons
***Low* potency statin combination therapy versus *high* potency statin monotherapy**									
Her, 2013 [28]	ATV/EZE 5/5 mg	Events	26	N/A	8 weeks	26	0(0)	NR	NR
Her, 2013 [28]	ATV20 mg	Events	25	N/A	8 weeks	25	0(0)	NR	NR
Lee, 2011[31]	ATV 20mg	CPK>10 X ULN	30	NR	8 weeks	30	N with events: 0,	NR	NR
Lee, 2011[31]	ATV 5mg +EZE 5mg	CPK>10 X ULN	30	NR	8 weeks	30	N with events: 0,	NR	NR
Lee, 2012[32]	ATV 20mg	CPK>10 X ULN	28	NR	8 weeks	28	N with events: 0,	NR	NR
Lee, 2012[32]	ATV 5mg +EZE 5mg	CPK>10 X ULN	32	NR	8 weeks	32	N with events: 0,	NR	NR
***Mid* potency statin combination therapy versus *high* potency statin monotherapy**									
Catapano, 2006 [15]	RSV 10 mg	CPK>10 X ULN	492	NR	6 weeks	NR	N with event(%)=0(0%)	NR	NR
Catapano, 2006 [15]	RSV 40 mg	CPK>10 X ULN	494	NR	6 weeks	NR	N with event(%)=1(0.1)	NR	NR
Catapano, 2006 [15]	RSV 20 mg	CPK>10 X ULN	495	NR	6 weeks	NR	N with event(%)=0(0%)	NR	NR
Catapano, 2006 [15]	EZE10/SMV20 mg	CPK>10 X ULN	492	NR	6 weeks	NR	N with event(%)=0(0%)	NR	NR
Foody, 2010[21]	ATV 20mg	CPK>10 X ULN	259	NR	12 weeks	246	N with events: 0, %with events: 0 ,	NR	NR
Foody, 2010[21]	ATV 40mg	CPK>10 X ULN	257	NR	12 weeks	248	N with events: 0, %with events: 0 ,	NR	NR

Foody, 2010[21]	SMV 20mg +EZE 10mg	CPK>10 X ULN	259	NR	12 weeks	250	N with events: 0, %with events: 0 ,	NR	NR
McKenny, 2007 [36]	RSV 20 mg	Elevations in CK>10x ULN	73	NR	12 weeks	NR	N=0	NR	NR
McKenney, 2007[36]	SMV/EZE (20/10)	Elevations in CK>10x ULN	72	NR	12 weeks	NR	N=0	NR	NR
Robinson, 2009[43]	ATV 20mg	CPK>10 X ULN	220	NR	6 weeks	220	%: 0, Counts: 0,	NR	NR
Robinson, 2009[43]	ATV 40mg	CPK>10 X ULN,	218	NR	6 weeks	218	%: 0, Counts: 0,	NR	NR
Robinson, 2009[43]	SMV 20mg +EZE10mg	CPK>10 X ULN	223	NR	6 weeks	223	%: 0.4, Counts: 1,	NR	NR
Stein, E, 2004 [46]	ATV 20	CPK>= 10X ULN	316	NR	12 weeks	316	Arm 1: N=1 %= <1	NR	NR
Stein, E, 2004 [46]	EZE+ATV (10/10)	CPK>= 10X ULN	305	NR	12 weeks	305	Arm 2: N=0 %=0	NR	NR
Zieve, 2010[48] Ben-Yehida, 2011[49]	ATV 20/40 mg	CPK>10 X ULN	527	NR	12 weeks	520	N=1	NR	NR
Zieve, 2010[48] Ben-Yehida, 2011[49]	ATV 10mg + EZE 10mg	CPK>10 X ULN	526	NR	12 weeks	526	N=0	NR	NR
***Low* potency statin combination therapy versus *mid* potency statin monotherapy**									
Feldman, 2004 [19]	SMV 20mg	CPK>10 X ULN	248	NR	23 weeks	248	N(%):2(0.8)	NR	NR
Feldman, 2004 [19]	SMV 10mg +EZE 10mg	CPK>10 X ULN	245	NR	23 weeks	245	N(%):0	NR	NR
Her, 2013 [28]	ATV/EZE 5/5 mg	CPK>10 X ULN	26	N/A	8 weeks	26	0(0)	NR	NR

Her, 2013 [28]	RSV10 mg	CPK>10 X ULN	25	N/A	8 weeks	25	0(0)	NR	NR

ATV Atorvastatin; CK Creatinine kinase; CPK Creatnine phospokinase; EZE Ezetimibe; N/A Not applicable; NR not reported; RSV Rosuvastatin; SMV simvastatin; ULN Upper normal limit

Evidence Table E21. Myalgia – general population

Author, Year	Arm	Outcome Units	Baseline N	Baseline Outcome	Timepoint (s)	N at Timepoint(s)	Outcomes at Timepoint(s)	Within Arm Comparisons	Between Arm Comparisons
Low ***potency statin combination therapy versus*** ***high*** ***potency statin monotherapy***									
Her, 2013 [28]	ATV20 mg	Events	25	N/A	8 weeks	25	1 (4)	NR	NR
Her, 2013 [28]	ATV/EZE 5/5 mg	Events	26	N/A	8 weeks	26	0(0)	NR	NR
Mid ***potency statin combination therapy versus*** ***high*** ***potency statin monotherapy – general population***									
Catapano, 2006 [15]	RSV 10mg	Experiencing myalgia	472	NR	12 weeks	472	0	NR	NR
Catapano, 2006 [15]	RSV 20mg	Experiencing myalgia	478	NR	12 weeks	478	0	NR	NR
Catapano, 2006 [15]	RSV 40mg	Experiencing myalgia	475	NR	12 weeks	475	N with event(%)=1	NR	NR
Catapano, 2006 [15]	SMV20mg +EZE 10mg	Experiencing myalgia	476	NR	12 weeks	476	0	NR	NR
Stein, E, 2004 [46]	ATV 20 mg	Myalgia	316	NR	12 weeks	316	Arm 1: %=9	NR	NR
Stein, E, 2004 [46]	EZE+ATV (10/10) mg	Myalgia	305	NR	12 weeks	305	Arm 2: %=8	NR	NR
Zieve, 2010[48] Ben-Yehida, 2011[49]	ATV 20/40mg	Participants with myalgia	NR	NR	12 weeks	525	%: 0, N with events: 0	NR	NR

Zieve, 2010[48] Ben-Yehida, 2011[49]	ATV 10mg + EZE10mg	Participants with myalgia	NR	NR	12 weeks	526	%: 0, N with events: 0	NR	NR
***Low* potency statin combination therapy versus *mid* potency statin monotherapy**									
Her, 2013 [28]	RSV 10 mg	Events	25	N/A	8 weeks	25	0(0)	NR	NR
Her, 2013 [28]	ATV/EZE 5/5 mg	Events	26	N/A	8 weeks	26	0(0)	NR	NR

ATV Atorvastatin; EZE Ezetimibe; N/A Not applicable; NR not reported; RSV Rosuvastatin; SMV simvastatin

Evidence Table E22. Mortality – patients with CHD

Author, Year	Arm	Outcome Units	Baseline N	Baseline Outcome	Timepoint (s)	N at Timepoint(s)	Outcomes at Timepoint(s)	Within Arm Comparisons	Between Arm Comparisons
***Mid* potency statin combination therapy versus *high* potency statin monotherapy**									
Roeters van Lennep, H.W.O,, 2007[44]	SMV 40mg (with SMV 20mg during run in)	Mortality	NR	NR	14 weeks	NR	0 deaths	NR	NR
Roeters van Lennep, H.W.O,, 2007[44]	ATV 20mg (with ATV10mg during run in)	Mortality	NR	NR	14 weeks	NR	0 deaths	NR	NR
Roeters van Lennep, H.W.O,, 2007[44]	SMV20 +EZE 10mg (with SMV 20 during run in)	Mortality	NR	NR	14 weeks	NR	0 deaths	NR	NR
Roeters van Lennep, H.W.O,, 2007[44]	SMV 20mg +EZE 10mg (with ATV 10mg during run in)	Mortality	NR	NR	14 weeks	NR	0 deaths	NR	NR

ATV Atorvastatin; EZE Ezetimibe; NR not reported; SMV simvastatin

Evidence Table E23. Acute coronary events – patients with CHD

Author, Year	Arm	Outcome Units	Baseline N	Baseline Outcome	Timepoint (s)	N at Timepoint(s)	Outcomes at Timepoint(s)	Within Arm Comparisons	Between Arm Compariso ns
***Mid* potency statin combination therapy versus *high* potency statin monotherapy**									
Ostad, 2009[40]	ATV 80mg	Fatal MI	NR	NR	8 weeks	24	N: 0	NR	NR
Ostad, 2009[40]	ATV 10mg + EZE10mg	Fatal MI	NR	NR	8 weeks	25	N: 1	NR	NR

ATV Atorvastatin; EZE Ezetimibe; MI Myocardial infarction; NR not reported; SMV simvastatin

Evidence Table E24. Cerebrovascular event – patients with CHD

RefID	Arm	Outcome Units	Baseline N	Baseline Outcome	Timepoint(s)	N at Timepoint(s)(s)	Outcomes at timepoint(s)	Within Arm Comparisons	Between arm comparisons
Mid potency statin combination therapy versus high potency statin monotherapy									
Averna, 2010[10]	SMV 40mg	Transient ischemic attack (TIA)	NR	NR	6 weeks	60	% with events:1.7, N with events: 1,	NR	NR
Averna, 2010[10]	SMV 20 +EZE 10 mg	Transient ischemic attack (TIA)	NR	NR	6 weeks	60	% with events: 0, N with events: 0	pvalue: NS , comparing	NR

EZE Ezetimibe; NR not reported; SMV simvastatin; TIA Transient ischemic attack

Evidence Table E25. Serious adverse event – patients with CHD

RefID	Arm	Outcome Units	Baseline N	Baseline Outcome	Timepoint(s)	N at Timepoint(s)(s)	Outcomes at timepoint(s)	Within Arm Comparisons
Mid potency statin combination therapy versus high potency statin monotherapy								
Averna, 2010[10]	SMV 40	Serious adverse events	NR	NR	6 weeks	60	%of with events: 1.7, N with events: 1	NR
Averna, 2010[10]	SMV 20 +EZE 10 mg	Serious adverse events	NR	NR	6 weeks	60	%of with events: 0, N with events: 0,	pvalue: NS , comparing Total vs Total at 6 weeks
Bardini, 2010[13]	SMV40	Serious adverse events	NR	NR	6 weeks	51	Counts: 0, %with events: 0 ,	
Bardini, 2010[13]	SMV 20mg +EZE 10mg	Serious adverse events	NR	NR	6 weeks	42	Counts: 1, %with vents:0.02 ,	pvalue: 0.4518 ,

								comparing Arm1 vs. Arm 2 at 6 weeks
Barrios, 2005 [14]	ATV 20	Serious adverse events	214	NR	6 weeks	205	N= 2 %= 0.9	p= 0.450
Barrios, 2005 [14]	EZE/SMV 10/20	Serious adverse events	221	NR	6 weeks	214	N= 5 %= 2.3	NR

ATV Atorvastatin; EZE Ezetimibe; NR not reported; SMV simvastatin

Evidence Table E26. LDL – patients with CHD

Author, Year	Arm	Outcome Units	Baseline N	Baseline Outcome	Timepoint (s)	N at Timepoint (s)	Outcomes at Timepoint(s)	Within Arm Comparisons	Between Arm Comparison
Mid *potency statin combination therapy versus high potency statin monotherapy*									
Averna, 2010[10]	SMV 40mg	LDLc, mg/dl Calculated	56	Mean: 128.0, SD: 16.6	6 weeks	56	NR	SE: +/- 1 , %change from baseline: -12	NR
Averna, 2010[10]	SMV 20mg +EZE10mg	LDLc, mg/dl Calculated	56	Mean: 125.9, SD: 16.3	6 weeks	56	NR	SE: +/- 1 , %change from baseline: -27,	p: <0.001 , comparing monotherapy vs combination weeks
Bardini, 2010[13]	SMV 40mg	LDLc mmol/L ,	50	Mean: 3.2, SD: 0.5	6 weeks	50	NR	% change from baseline:-21	NR
Bardini, 2010[13]	SMV 20mg +EZE10mg	LDLc mmol/L ,	37	Mean: 3.3, SD: 0.5	6 weeks	37	NR	% change from baseline:-32, p<0.01	NR
Barrios, 2005[14]	ATV 20mg	Continuous LDLc mg/dl calculated	214	Mean: 3.24 SD: 0.49	6 weeks	207-210	NR	Mean % change:-20.3 SE: 1.2 0 weeks vs. 6 weeks	Diff. in least squares % change: -12.6 SE: 1.6 P <0.001 0 weeks vs. 6 weeks
Barrios, 2005[14]	SMV 20mg +EZE10mg	Continuous LDLc mg/dl calculated	221	Mean: 3.19 SD: 0.45	6 weeks	215-217	NR	Mean % change: -32.8 SE: 1.2	NR
Cho, 2011[16]	ATV 20 mg	LDLc mg/dl	43	Mean: 132.1, SD: 30.6, ,	6 weeks	NR	Mean: 72.9, SD: 20.5, ,	% change from baseline:41.1, SD:17.3	NR
Cho, 2011[16]	SMV 20mg +EZE10mg	LDLc mg/dl	42	Mean: 134.1, SD: 23.2, ,	6 weeks	NR	Mean: 77.2, SD: 21.0, ,	% change from baseline:44.2, SD:14.0	p: 0.715 , at 6 weeks p: 0.759 ,

Author, Year	Arm	Outcome Units	Baseline N	Baseline Outcome	Timepoint (s)	N at Timepoint (s)	Outcomes at Timepoint(s)	Within Arm Comparisons	Between Arm Comparison
									at baseline comparing monotherapy vs combination
Hamdan, 2011[27]	ATV 20 mg + placebo	LDLc mg/dl	44	Mean: 3.4	12weeks	34	Mean: 2.1mmol/L Mean: 2.1 mmol/L	% change from baseline (calculated, not reported) -38.2	NR NR
Hamdan, 2011[27]	ATV10mg +EZE10mg	LDLc mg/dl	43	Mean: 3.2	12weeks	41	Mean: 1.6 mmol/L Mean: 1.8 mmol/L	% change from baseline: -43.8 (calculated, not reported)	group x time: p=0.6, Comparing total vs. total at 12 weeks
Matsue, 2013 [35]	EZE/ATV 10/10 mg	Mg/dL	115	Mean: 94.4 SD: 16.8	12 weeks	115	Mean:69.6 SD: 15.6	P<0.001 P<0.001 Percent change (calculated) - 26.3%	NR
Matsue, 2013 [35]	ATV 20 mg	Mg/dL	128	Mean: 95.1 SD: 18.4	12 weeks	128	Mean: 85.9 SD: 18.2	P<0.001 Percent change (calculated) -9.6%	
Okada, 2011[39]	ATV 20 mg	LDLc mg/dl. measured	35	Mean: 114.1, SD: 14.7	12weeks	35	Mean: 94.5, SD: 16.8	% change from baseline : -17.1 (calculated, not reported)	NR
Okada, 2011[39]	RSV 5 mg	LDLc mg/dl	38	Mean: 120.3, SD: 18.4	12weeks	38	Mean: 101.5, SD: 22.5	% change from baseline: -15.6 (calculated, not reported)	NR
Okada, 2011[39]	ATV 10mg +EZE10mg	LDLc mg/dl	43	Mean: 120.5, SD: 16.9	12weeks	43	Mean: 89.1, SD: 15.8	% change from baseline:-26.1 (calculated, not reported)	NR
Okada, 2011[39]	RSV 2.5mg +EZE10mg	LDLc mg/dl	49	Mean: 120.0 , SD: 13.1	12weeks	49	Mean: 91.3, SD: 17.8	% change from baseline:-23.9 (calculated, not reported)	NR

Author, Year	Arm	Outcome Units	Baseline N	Baseline Outcome	Timepoint (s)	N at Timepoint (s)	Outcomes at Timepoint(s)	Within Arm Comparisons	Between Arm Comparison
Ostad, 2009[40]	ATV 80mg	LDLc	24	Mean: 148, SD: 31	8 weeks	NR	Mean: 59,SD: 21,	Mean difference= -60, SD= 11, p<0.001	NR
Ostad, 2009[40]	ATV 10mg +EZE10mg	LDLc	25	Mean: 151, SD: 31	8 weeks	NR	Mean: 67,SD: 27,	Mean difference= -54, SD= 18, p=0.001	p: 0.5 , at 8 weeks p: 0.73 , at baseline comparing monotherapy vs combination
Pesaro, 2012[41]	SMV 80mg	LDLc mg/dl ,	38	Median: 101, IQR: 85-130	6weeks	38	Median: 76, IQR: 61-90	% mean change: -28, SD:30, P<0.01	NR
Pesaro, 2012[41]	SMV 20mg +EZE10mg	LDLc mg/dl ,	40	Median: 99, IQR: 89-117	6weeks	40	Median: 72, IQR: 62-80	% mean change: 29, SD:13, p<0.01	p: 0.46 , at 6 weeks p: 0.83 , at baseline comparing monotherapy vs combination
Piorkowski, 2007[42]	ATV 40mg	LDLc mmol/l calculated	25	Mean:3.49 SD:0.18	4 weeks	25	Mean:2.48, SD:0.11	% change, calculated,(not reported): -28.9 p<0.005 before vs. after	Diff. in change from baseline: monotherapy vs combination; p=ns
Piorkowski, 2007[42]	ATV 10mg +EZE10mg	LDLc mmol/l calculated	26	Mean:3.61 SD:0.22	4 weeks	26	Mean:2.25, SD:0.16	% change, calculated, not reported : -37.7 p<0.005 before vs. after	NR
Yamazaki,	RSV 10 mg	LDLc	24	Mean: 88.5,	4weeks	NR	Mean: 68.0,	0 vs. 4 wks,	NR

Author, Year	Arm	Outcome Units	Baseline N	Baseline Outcome	Timepoint (s)	N at Timepoint (s)	Outcomes at Timepoint(s)	Within Arm Comparisons	Between Arm Comparison
2013[47]		mg/dl, measured		SD: 12.9			SD: 13.9	p<0.0001	
					8 weeks	NR	Mean: 65.3, SD: 18.0	0 vs. 8 wks, p<0.0001	
					12 weeks	NR	Mean: 67.9, SD: 17.0	0 vs.12 wks: -20.3 +/- 15.3, p<0.0001	
Yamazaki, 2013[47]	RSV 2.5mg +EZE10mg	LDLc mg/dl, measured	22	Mean: 84.3, SD: 14.5	4 weeks	NR	Mean: 62.3, SD: 12.2	0 vs. 4 wks, p<0.0001	NR
					8 weeks	NR	Mean: 62.6, SD: 15.3	0 vs. 8 wks, p<0.0001	
					12 weeks	NR	Mean: 62.9, SD: 11.7	0 vs. 12 wks= -21.9 +/- 14.4, p <0.0001	

ATV atorvastatin; EZE Ezetimibe; HCL higher confidence limit; IQR interquartile range; LCL lower confidence limit; LDLc low density lipoprotein cholesterol; LOV Lovastatin; NR not reported; NS Not significant; SD standard deviation; SE standard error; SMV simvastatin;

Evidence Table E27. HDL-c – patients with CHD

Author, Year	Arm	Outcome Units	Baseline N	Baseline Outcome	Timepoint (s)	N at Timepoint(s)	Outcomes at Timepoint(s)	Within Arm Comparisons	Between Arm Comparisons
Mid potency statin combination therapy versus high potency statin monotherapy									
Averna, 2010[10]	SMV 40mg	HDLc, mg/dl Measured	56	Mean: 48.8, SD: 9.2	6weeks	56	SE: +/- 2 , %change from baseline: -1,	NR	NR
Averna, 2010[10]	SMV 10mg +EZE 10mg	HDLc mg/dl , Measured	56	Mean: 50.5, SD: 11.4	6 weeks	56	SE: +/- 2 , %change from baseline: 2	NR	p: ns monotherapy vs combination at 6 weeks
Bardini, 2010[13]	SMV 40mg	HDLc	50	NR	0 week	50	Mean: 1.1, SD: 0.3	% change from baseline: 0.8	NR
Bardini, 2010[13]	SMV 20mg +EZE 10mg	HDLc	37	NR	0 week	37	Mean: 1.2, SD: 0.3	% change from baseline:0.9	NR
Barrios, 2005[14]	ATV 20mg	Continuous HDLc mg/dL measured	214	Mean: 1.44 SD: 0.35	6 weeks	207-210	NR	Mean per cent change: -0.4 SE: 0.8 0 weeks vs. 6 weeks	Difference in least squares per cent change: +2.5 SE: 1.2 p: <0.05 0 weeks vs. 6 weeks
Barrios, 2005[14]	SMV 20mg +EZE10mg	Continuous HDLc mg/dl measured	221	Mean: 1.38 SD: 0.31	6 weeks	215-217	NR	Mean per cent change: +1.8 SE: 0.8	NR
Cho, 2011[16]	ATV 20 mg	HDLc	43	Mean: 46.1, SD: 9.8,	6weeks	NR	Mean: 46.9, SD: 13.2	% change from baseline:-2.3, SD:26.6	NR
Cho, 2011[16]	SMV 20mg +EZE 10 mg	HDLc	42	Mean: 45.2, SD: 9.8,	6weeks	NR	Mean: 46.4, SD: 9.0	% change from baseline:-4.4, SD:17.8	p: 0.699 , at 6 weeks p: 0.704 ,at baseline monotherapy vs combination

Hamdan, 2011[27]	ATV 20 mg +placebo	HDLc mmol/L	44	Mean: 0.9	12 weeks	34	Mean: 0.9 SD: 1.0	NR	NR
Hamdan, 2011[27]	ATV 10mg +EZE 10mg	HDLc mmol/L	43	Mean: 0.9	12weeks	41	Mean: 0.8 SD: 0.9	NR	group x time: p=0.2 , total vs. total at 12 weeks
Matsue, 2013 [35]	EZE/ATV 10/10 mg	Mg/dL	115	Mean:52.4 SD:11.9	12 weeks	115	Mean:51.8 SD:10.8	% change (calculated)= -1.1% P=0.292	NR
Matsue, 2013 [35]	ATV 20 mg	Mg/dL	128	Mean:50.7 SD:11.7	12 weeks	128	Mean:50.2 SD:12.1	% change (calculated)= -1% P=0.337	
Okada, 2011[39]	RSV 5 mg	HDLc mg/dl	38	Mean: 49.6, SD: 10.2	12 weeks	38	Mean: 51.0, SD: 12.8	NR	p: ns , Mean diff: NR , SD: NR
Okada, 2011[39]	ATV 10mg +EZE 10 mg	HDLc mg/dl ,	43	Mean: 52.9, SD: 9.1	12 weeks	43	Mean: 53.5, SD: 13.4	NR	p: ns , Mean diff: NR , SD: NR
Okada, 2011[39]	ATV 20 mg	HDLc mg/dl	35	Mean: 50.9, SD: 9.9	12 weeks	35	Mean: 47.7, SD: 9.8	NR	p: ns , Mean diff:NR , SD: NR
Okada, 2011[39]	RSV 2.5mg +EZE 10 mg	HDLc mg/dl ,	49	Mean: 51.4, SD: 13.5	12 weeks	49	Mean: 53.0, SD: 13.9	NR	p: ns , Mean diff: NR , SD: NR
Ostad, 2009[40]	ATV 80mg	HDLc	24	Mean: 52, SD: 9	8weeks	NR	Mean: 53, SD: 10	mean relative change %:4, SD:15, P:0.31	NR
Ostad, 2009[40]	ATV 10mg + EZE 10mg	HDLc	25	Mean: 58, SD: 17	8weeks	NR	Mean: 58, SD: 16	mean relative change %:2, SD:15, P:0.69	p: 0.7 ,at 8 weeks p: 0.14 ,at baseline monotherapy vs combination
Pesaro, 2012[41]	SMV 80mg	HDLc	38	Median: 45, IQR: 38-50	6weeks	38	Median: 42, IQR: 38-48	% mean change:-1%, SD: 14, P:0.16	NR
Pesaro, 2012[41]	SMV 20mg +EZE 10mg	HDLc	40	Median: 42, IQR: 37-48	6weeks	40	Median: 43, IQR: 38-49,	% mean change: 2%, SD:11, p:0.38	NR

Piorkowski, 2007[42]	ATV 40mg	HDLc mmol/l calculated	25	Mean:1.31 SD:0.07	4 weeks	25	Mean:1.27, SD:0.07	NR	NR
Piorkowski, 2007[42]	ATV 10mg +EZE 10mg	HDLc mmol/l calculated	26	Arm 2: Mean:1.39 SD:0.07	4 weeks	26	Mean:1.33, SD:0.08	NR	NR
Yamazaki, 2013[47]	RSV10mg	HDLc mg/dl measured	24	Mean: 46.4, SD: 11.6	4 weeks 8 weeks 12 weeks	NR	Mean: 47.8, SD: 10.3 Mean: 51.0, SD: 10.3 Mean: 51.5, SD: 12.1	NR $p<0.05$, 8 weeks vs. 0 weeks; Mean difference:4.6, SD: 5.9, $p<0.05$, 12 weeks vs. 0 weeks	NR
Yamazaki, 2013[47]	RSV 2.5mg +EZE10mg	HDLc mg/dl	22	Mean: 49.9, SD: 12.2	4 weeks 8 weeks 12 weeks	NR	Mean: 51.0, SD: 10.0 Mean: 51.7, SD: 11.0 Mean: 51.0, SD: 9.1	NR NR Mean diff .:0, SD: 6.7 12 weeks vs. 0 weeks	$p<0.05$, Mean change monotherapy vs combination at 12 weeks

ATV atorvastatin; EZE Ezetimibe; HCL higher confidence limit; HDLc High density lipoprotein cholesterol; IQR interquartile range; LCL lower confidence limit; LOV Lovastatin; NR not reported; NS Not significant; SD standard deviation; SE standard error; SMV simvastatin;

Evidence Table E28. Total cholesterol:HDL-c – patients with CHD

Author, Year	Arm	Outcome Units	Baseline N	Baseline Outcome	Timepoint (s)	N at Timepoint(s)	Outcomes at Timepoint(s)	Within Arm Comparisons	Between Arm Comparisons
***Mid* potency statin combination therapy versus *high* potency statin monotherapy**									
Barrios, 2005[14]	ATV 20mg	Continuous TC:HDLc	214	Mean: 3.92, SD: 0.86	6 weeks	207-210	NR	Mean per cent change:-11.7 SE: 1.0 0 weeks vs. 6 weeks	Diff. in least squares % change: -9.3 SE: 1.4 p: <0.001 0 weeks vs. 6 weeks
Barrios, 2005[14]	SMV 20mg +EZE 10mg	Continuous TC:HDLc	221	Mean: 3.99, SD: 0.83	6 weeks	215-217	NR	Mean per cent change: -20.9 SE: 1.0	NR

ATV atorvastatin; EZE Ezetimibe; HDLc High density lipoprotein cholesterol; NR not reported; NS Not significant; SD standard deviation; SE standard error; SMV simvastatin; TC Total cholesterol

Evidence Table E29. Adherence – patients with CHD

Author, Year	Arm	Outcome Units	Baseline N	Baseline Outcome	Timepoint (s)	N at Timepoint(s)	Outcomes at Timepoint(s)	Within Arm Comparisons	Between Arm Comparisons
***Mid* potency statin combination therapy versus *high* potency statin monotherapy**									
Bardini, 2010[13]	SMV40	Treatment adherence	51	NR	6 weeks	51	Counts: 2,	NR	NR
Bardini, 2010[13]	SMV 20/ EZE 10mg	Treatment adherence	42	NR	6 weeks	42	Counts: 1,	NR	NR
Cho, 2011[16]	ATV 20 mg	Treatment adherence	43	NR	6 weeks	NR	compliance %: >99 ,	NR	NR
Cho, 2011[16]	SMV/EZE (20/10 mg)	Treatment adherence	42	NR	6 weeks	NR	compliance %: >99 ,	NR	NR

ATV atorvastatin; EZE Ezetimibe NR not reported; SMV simvastatin;

Evidence Table E30. Any adverse event – patients with CHD

Author, Year	Arm	Outcome Units	Baseline N	Baseline Outcome	Timepoint (s)	N at Timepoint(s)	Outcomes at Timepoint(s)	Within Arm Comparisons	Between Arm Comparisons
***Mid* potency statin combination therapy versus *high* potency statin monotherapy**									
Averna, 2010[10]	SMV 40mg	At least one adverse event	60	NR	6 weeks	60	N(%)of patient with events: 13(21.7),	NR	NR
Averna, 2010[10]	SMV 20mg + EZE 10mg	At least one adverse event	60	NR	6 weeks	60	N(%)of patient with events: 13(21.7)		p: 0.9999 , comparing monotherapy vs. combination at 6 weeks
Bardini, 2010[13]	SMV 40mg	At least one adverse event	51	NR	6 weeks	51	N(%) with events: 10(20),	NR	NR
Bardini, 2010[13]	SMV 20mg EZE10mg	,At least one adverse event	42	NR	6 weeks	42	N(%) with events: 5(12.5)	NR	p:0.40008 comparing monotherapy vs. combination at 6 weeks
Barrios, 2005[14]	ATV 20mg	At least one adverse event	214	NR	6 weeks	205	N(%)with events:51(23.8)	NR	p: 0.354
Barrios, 2005[14]	SMV20 +EZE 10mg	At least one adverse event	221	NR	6 weeks	214	N(%)with events:44(19.9)	NR	NR

ATV atorvastatin; EZE Ezetimibe NR not reported; SMV simvastatin;

Evidence Table E31. Withdrawal due to adverse events – patients with CHD

Author, Year	Arm	Outcome Units	Baseline N	Baseline Outcome	Timepoint (s)	N at Timepoint(s)	Outcomes at Timepoint(s)	Within Arm Comparisons	Between Arm Comparisons
***Mid** potency statin combination therapy versus **high** potency statin monotherapy*									
Averna, 2010[10]	SMV 40mg	Withdrawal due to adverse events ,	60	NR	6 weeks	60	%of patient with events: 1.7, N patients with events: 1,	NR	NR
Averna, 2010[10]	SMV 20mg +Ezetimibe10mg	Withdrawal due to adverse events ,	60	NR	6 weeks	60	%of patient with events: 0, N patients with events: 0,	NR	pvalue: NS monotherapy vs. combination
Bardini, 2010[13]	SMV40	Withdrawal due to adverse events ,	51	NR	6 weeks	51	Counts: 2, %with events: 4 ,	NR	NR
Bardini, 2010[13]	SMV 20/ EZE10mg	Withdrawal due to adverse events ,	42	NR	6 weeks	42	Counts: 1, %with events: 2.5 ,	NR	pvalue: 0.9999 comparing monotherapy vs. combination
Barrios, 2005[14]	EZE/SMV 10/20	Withdrawal due to adverse events	214	NR	6 weeks	205	N=8 %=3.7	NR	NR
Barrios, 2005[14]	EZE/SMV 10/20	Withdrawal due to adverse events	221	NR	6 weeks	214	N=5 %=2.3	NR	p=0.41
Hamdan, 2011[27]	ATV 20 mg	Withdrawal due to adverse events	46	NR	12 weeks	NR	Counts: 10, proportion: 22.2%	NR	NR
Hamdan, 2011[27]	ATV/EZE 10/10 mg	Withdrawal due to adverse events	47	NR	12 weeks	NR	Counts: 2, proportion: 4.3%	NR	p=0.012 , Comparing total vs total at 12 weeks
Ostad, 2009[40]	ATV 80mg	Withdrawal due to adverse events ,	NR	NR	8 weeks	NR	Counts: 5,	NR	NR

Ostad, 2009[40]	ATV 10mg + EZE 10mg	Withdrawal due to adverse events	NR	NR	8 weeks	NR	Counts: 2,	NR	NR

ATV atorvastatin; EZE Ezetimibe NR not reported; SMV simvastatin;

Evidence Table E32. Elevated liver transaminases – patients with CHD

Author, Year	Arm	Outcome Units	Baseline N	Baseline Outcome	Timepoint (s)	N at Timepoint(s)	Outcomes at Timepoint(s)	Within Arm Comparisons	Between Arm Comparisons
***Mid* potency statin combination therapy versus *high* potency statin monotherapy**									
Averna, 2010[10]	SMV 40mg	Elevated AST and/or ALT > 3x ULN and/or hepatitis	60	NR	6 weeks	60	N(%)with events:0(0)	NR	NR
Averna, 2010[10]	SMV +EZE	Elevated AST and/or ALT > 3x ULN and/or hepatitis	60	NR	6 weeks	60	N(%)with events:0(0)	NR	NR
Bardini, 2010[13]	SMV 40mg	Elevated AST and/or ALT > 3x ULN and/or hepatitis	51	NR	6 weeks	51	N(%)with events:0(0)	NR	NR
Bardini, 2010[13]	SMV 20mg +EZE 20mg	Elevated AST and/or ALT > 3x ULN and/or hepatitis	42	NR	6 weeks	42	N(%)with events:0(0)	NR	NR
Barrios, 2005[14]	ATV 20mg	Elevated AST/ALT ≥ 3x ULN	214	NR	6 weeks	205	N(%)with event:0(0)	NR	p:1.00
Barrios, 2005[14]	SMV 20mg +EZE 10mg	Elevated AST/ALT≥3x ULN	221	NR	6 weeks	217	N(%)with event:1(0.5)	NR	NR

Cho, 2011[16]	ATV 20 mg	Elevated AST and/or ALT > 3x ULN and/or hepatitis	43	NR	6 weeks	NR	N(%)with events:1(2.6)	NR	NR
Cho, 2011[16]	SMV 20mg +EZE 10 mg	Elevated AST and/or ALT > 3x ULN and/or hepatitis	42	NR	6 weeks	NR	N(%)with events:0(0)	NR	NR
Hamdan, 2011[27]	ATV 20 mg	Elevated AST and/or ALT > 3x ULN and/or hepatitis	46	N: 0	12 weeks	NR	NR	NR	NR
Hamdan, 2011[27]	ATV 10mg +EZE 10mg	Elevated AST and/or ALT > 3x ULN and/or hepatitis	47	N: 0	12 weeks	NR	NR	NR	p:0.8, comparing total vs. total at 12 weeks
Pesaro, 2012[41]	SMV 80mg	Elevated AST and/or ALT > 3x ULN and/or hepatitis,	38	NR	6 weeks	38	N with events: 0	NR	NR
Pesaro, 2012[41]	SMV 20mg +EZE 10mg	Elevated AST and/or ALT > 3x ULN and/or hepatitis	40	NR	6 weeks	40	N with events: 0	NR	NR

ALT Alanine transaminase; AST Aspartate transaminase; ATV Atorvastatin; CHD Cardiovascular heart disease; EZE Ezetimibe; N/A Not applicable; NR not reported; RSV Rosuvastatin; SMV simvastatin; ULN Upper normal limit

Evidence Table E33. Musculoskeletal adverse events – patients with CHD

Author, Year	Arm	Outcome Units	Baseline N	Baseline Outcome	Timepoint (s)	N at Timepoint(s)	Outcomes at Timepoint(s)	Within Arm Comparisons	Between Arm Comparisons
***Mid* potency statin combination therapy versus *high* potency statin monotherapy**									
Averna, 2010[10]	SMV +EZE	CK elevated >=10 X ULN	60	NR	6 weeks	60	%of patient with events: 0, N patients with events: 0	NR	NR
Bardini, 2010[13]	SMV 40mg	CK elevated >=10 X ULN	60	NR	6 weeks	60	% of patient with events: 0, N patients with events: 0,	NR	NR
Bardini, 2010[13]	SMV 40mg	CK elevated >=10 X ULN	51	NR	6 weeks	51	Counts: 0, %with events: 0 ,	NR	NR
Bardini, 2010[13]	SMV 20mg +EZE 20mg	CK elevated >=10 X ULN	42	NR	6 weeks	42	Counts: 0, %with events: 0 ,	NR	NR
Barrios, 2005[14]	ATV 20 mg	CK elevated >=10 X ULN	214	NR	6 weeks	205	N=0 %=0	NR	NR
Barrios, 2005[14]	EZE/SMV 10/20 mg	CK elevated >=10 X ULN	221	NR	6 weeks	214	N=0 %=0	NR	NR
Cho, 2011[16]	ATV 20 mg	CK elevated >=10 X ULN	43	NR	6 weeks	NR	N. with events: 0, %with events: 0 ,	NR	NR
Cho, 2011[16]	SMV 20mg +EZE 10 mg	CK elevated >=10 X ULN	42	NR	6 weeks	NR	N with events: 0, %with events: 0 ,	NR	NR

ATV Atorvastatin; CHD Cardiovascular heart disease; CK creatinine kinase; EZE Ezetimibe; N/A Not applicable; NR not reported; RSV Rosuvastatin; SMV simvastatin; ULN Upper normal limit

Evidence Table E34. Myalgia – patients with CHD

Author, Year	Arm	Outcome Units	Baseline N	Baseline Outcome	Timepoint (s)	N at Timepoint(s)	Outcomes at Timepoint(s)	Within Arm Comparisons	Between Arm Comparisons
Mid potency statin combination therapy versus high potency statin monotherapy									
Pesaro, 2012[41]	SMV 80	myalgia	NR	NR	6 weeks	38	Counts: 0	NR	NR
Pesaro, 2012[41]	SMV 20+ EZE 10mg	myalgia	NR	NR	6 weeks	40	Counts: 0	NR	NR

EZE Ezetimibe; NR not reported; SMV simvastatin;

Evidence Table E35. Mortality – patients with diabetes mellitus

Author, Year	Arm	Outcome Units	Baseline N	Baseline Outcome	Timepoint (s)	N at Timepoint(s)	Outcomes at Timepoint(s)	Within Arm Comparisons	Between Arm Comparisons
Mid potency statin combination therapy versus high potency statin									
Constance, 2007[17]	ATV 20mg	All-cause mortality	219	NR	6 weeks	219	N(%)=1(0.50	NR	NR
Constance, 2007[17]	SMV 20mg+EZE 10mg	All-cause mortality	220	NR	6 weeks	220	N(%)=0	NR	NR
Roeters van Lennep, H.W.O,, 2007[44]	Statin doubling	Mortality	189	NR	14 weeks	189	N=0 %=0	NR	NR
Roeters van Lennep, H.W.O,, 2007[44]	combination arms	Mortality	178	NR	14 weeks	178	N=0 %=0	NR	NR

ATV; Atorvastatin; EZE Ezetimibe; NR not reported; SMV simvastatin;

Evidence Table E36. Serious adverse events – patients with diabetes mellitus

Author, Year	**Arm**	**Outcome Units**	**Baseline N**	**Baseline Outcome**	**Timepoint (s)**	**N at Timepoint (s)**	**Outcomes at Timepoint(s) N(%)**	**Within Arm Comparisons**	**Between Arm Comparison**
Mid potency statin combination therapy versus high potency statin monotherapy									
Bardini, 2010[13]	SMV40	Serious adverse events	NR	NR	6 weeks	51	Counts: 0, %with events: 0 ,	NR	NR
Bardini, 2010[13]	SMV 20mg +EZE 10mg	Serious adverse events	NR	NR	6 weeks	42	Counts: 1, %with vents:0.02 ,	NR	pvalue: 0.4518 , comparing monotherapy vs. combination
Constance, 2007[17]	ATV 20mg	Serious Adverse Event	219	NR	6 weeks	219	N(%)=5(2.3)	NR	NR
Constance, 2007[17]	SMV 20mg +EZE 10mg	Serious Adverse Event	220	NR	6 weeks	220	N(%)=1(0.5)	NR	NR
Foody, 2010[21]	ATV 20mg	Serious adverse events	NR	NR	12 weeks	258	N with events: 3, %with events: 1.2 ,	NR	NR
Foody, 2010[21]	ATV 40mg	Serious adverse events	NR	NR	12 weeks	256	N with events: 5, %with events: 2 ,	NR	NR

Foody, 2010[21]	SMV 20mg +EZE 10mg	Serious adverse events	NR	NR	12 weeks	256	N with events: 8, % with events:3.1	NR	NR
Gaudiani, 2005 [22]	SMV 40mg	Serious Adverse Event	110	NR	24 weeks	110	N=1(0.9%)	NR	NR
Gaudiani, 2005 [22]	SMV 20mg +EZE 10mg	Serious Adverse Event	104	NR	24 weeks	104	N=5(4.8%)	NR	NR
Lee, 2013 [33]	EZE/SMV 10/20 mg	Serious Adverse Event	66	NR	12 weeks	62	0 (0)	NR	NR
Lee, 2013 [33]	ATV 20	Serious Adverse Event	66	NR	12 weeks	63	0 (0)	NR	NR

ATV; Atorvastatin; EZE Ezetimibe; NR not reported; SMV simvastatin;

Evidence Table E37. LDL – patients with diabetes mellitus

Author, Year	Arm	Outcome Units	Baseline N	Baseline Outcome	Timepoint (s)	N at Timepoint (s)	Outcomes at Timepoint(s)	Within Arm Comparisons	Between Arm Comparison
***Low** potency statin combination therapy versus **high** potency statin monotherapy*									
Rudofsky, 2012[45]	SMV80mg	LDLc , calculated	10	Median: 151	8 weeks	10	Median: 74	median change from baseline:-77, % change from baseline (calculated, not reported) :51.0 Pvalue:0.005	NR
Rudofsky, 2012[45]	SMV10mg +EZE10mg	LDLc calculated	11	Median: 154	8 weeks	11	Median: 68	median change from baseline: -86, % change from baseline (calculated, not reported) :55.8 pvalue:0.003	P value: 0.40 , Comparing monotherapy to combination
***Mid** potency statin combination therapy versus **high** potency statin monotherapy*									
Bardini, 2010[13]	SMV 40mg	LDLc mmol/L ,	50	Mean: 3.2, SD: 0.5	6 weeks	50	NR	% change from baseline:-21	NR
Bardini, 2010[13]	SMV 20mg +EZE10mg	LDLc mmol/L ,	37	Mean: 3.3, SD: 0.5	6 weeks	37	NR	% change from baseline:-32, p<0.01	NR
Barrios, 2005[14]	ATV 20mg	LDLc DM Subgroup	53	NR	6 weeks	NR	NR	Mean % change in LDL from baseline: -24 SE:3	NR
Barrios, 2005[14]	SMV 20mg +EZE10mg	LDLc DM subgroup	59	NR	6 weeks	NR	NR	Mean % change in LDL from baseline: -34 SE:3	NR
Constance, 2007[17]	ATV 20mg	LDLc mmol/l calculated	219	Mean: 2.43 SD: 0.69	6 weeks	213	NR	Least squares mean% change(SD):-8.49(26.83)	NR
Constance,	SMV 20mg	LDLc	220	Mean: 2.34	6 weeks	210	NR	Least squares	p≤0.001

Author, Year	Arm	Outcome Units	Baseline N	Baseline Outcome	Timepoint (s)	N at Timepoint (s)	Outcomes at Timepoint(s)	Within Arm Comparisons	Between Arm Comparison
2007[17]	+EZE10mg	mmol/l calculated		SD: 0.69				mean % change Least squares (SD): -26.15(26.89)	comparing monotherapy to combination
Foody, 2010[21]	ATV 20mg	LDLc mg/dl , DIABETICS	NR	NR	NR	NR	NR	% change from baseline:-40, SE:3	NR
Foody, 2010[21]	ATV 40mg	LDLc mg/dl , DIABETICS	NR	NR	NR	30	NR	% change from baseline:-48, SE:2	NR
Foody, 2010[21]	SMV 20mg +EZE10mg	LDLc mg/dl , DIABETICS	NR	NR	NR	NR	NR	% change from baseline: -52, SE:2	NR
Gaudiani, 2005[22]	SMV 40mg	Continuous LDLc mmol/l Measured	110	Mean: 2.37 SD: 0.63	24 weeks	107	Absolute reduction: -0.04	Least square mean % change (SD) : -0.3(22.8)	Diff. in mean % change from baseline: -20.5 p<0.001 comparing monotherapy to combination
Gaudiani, 2005[22]	SMV 20mg +EZE10mg	Continuous LDLc mmol/l measured	104	Mean: 2.43 SD: 0.74	24 weeks	103	Absolute reduction: -0.52	Least square mean% change(SD): -20.8(22.3)	NR
Goldberg, 2006[24] Tomassini, 2009[25] Guyton, 2008[26]	ATV20 mg	Continuous LDLc mg/dl	245	Mean: 146.6	6 weeks	240	NR	% Change from baseline: -44.6	Treatment diff: -9.0 p<0.001, Vs. combination
Goldberg, 2006[24] Tomassini, 2009[25]	Arm 2: ATV 40mg	Continuous LDLc mg/dl	245	Mean: 145.9	6 weeks	241	NR	% Change from baseline: -50.9	NR

Author, Year	Arm	Outcome Units	Baseline N	Baseline Outcome	Timepoint (s)	N at Timepoint (s)	Outcomes at Timepoint(s)	Within Arm Comparisons	Between Arm Comparison
Guyton, 2008[26]									
Goldberg, 2006[24] Tomassini, 2009[25] Guyton, 2008[26]	SMV 20mg +EZE10mg	Continuous LDLc mg/dl	247	Mean: 145.0	6 weeks	238	NR	% Change from baseline: -53.6	NR
Lee, 2013 [33]	EZE/SMV 10/20 mg	Mg/dL	66	Mean: 139.3 SD:26.8	12 weeks	62	Mean: 72.6 SD:32.1	% change= -47.9 SD= 20.7 P<0.05	P=0.234
Lee, 2013 [33]	ATV 20mg	Mg/dL	66	Mean: 133.8 SD: 30.1	12 weeks	63	Mean: 70.1 SD: 24.6	% change= -47.2 SD= 15.6 P<0.05	
Zieve, 2010[48] Ben-Yehida, 2011[49]	ATV 20mg/40mg	LDLc mg/dl , Measured T2DM	113	NR	12 weeks	107	SE: 4 , ,%change from baseline: -20,	NR	NR
Zieve, 2010[48] Ben-Yehida, 2011[49]	ATV10mg +EZE10mg	LDLc mg/dl , Measured T2DM	110	NR	12 weeks	106	SE: 4 , ,%change from baseline: -26 ,	NR	NR
Low ***potency statin combination therapy versus*** ***mid*** ***potency statin monotherapy***									
Kawagoe, 2011[29]	FLV 60mg	LDLc mg/dl , All Participants Have DM	12	Mean: 154 SD: 26	10	12	Mean: 106, SD: 15	%change from baseline (calculated, not reported) :31.2 Mean difference: 64.8 SD: 17.3 P value:<0.005	NR
Kawagoe, 2011[29]	FLV 20mg +EZE10mg	LDLc mg/dl , All Participants Have DM	12	Mean: 164 SD: 33	10	12	Mean: 96, SD: 22	percent change from baseline (calculated, not reported) :41.5 Mean diff.: 42.7 SD: 22.7	p<0.05, at 10 weeks,

Author, Year	Arm	Outcome Units	Baseline N	Baseline Outcome	Timepoint (s)	N at Timepoint (s)	Outcomes at Timepoint(s)	Within Arm Comparisons	Between Arm Comparison
								p <0.005	

ATV atorvastatin; EZE Ezetimibe; FLV Fluvastatin; LDLc low density lipoprotein cholesterol; NR not reported; NS Not significant; SD standard deviation; SE standard error; SMV simvastatin;

Evidence Table E38. HDL-c – patients with diabetes mellitus

Low potency statin combination therapy versus high potency statin monotherapy

Author, Year	Arm	Outcome Units	Baseline N	Baseline Outcome	Timepoint (s)	N at Timepoint(s)	Outcomes at Timepoint(s)	Within Arm Comparisons	Between Arm Comparisons
Rudofsky, 2012[45]	SMV 80mg	HDLc mg/dl	10	Median: 45	8 weeks	10	Median: 42	p:0.44 0 weeks vs. 8 weeks	NR
Rudofsky, 2012[45]	SMV 10mg +EZE 10mg	HDLc mg/dl	11	Median: 46	8 weeks	11	Median: 46	p=0.82 0 weeks vs. 8 weeks	NR
Mid potency statin combination therapy versus high potency statin monotherapy									
Bardini, 2010[13]	SMV 40mg	HDLc	50	NR	0 week	50	Mean: 1.1, SD: 0.3	% change from baseline: 0.8	NR
Bardini, 2010[13]	SMV 20mg +EZE 10mg	HDLc	37	NR	0 week	37	Mean: 1.2, SD: 0.3	% change from baseline:0.9	NR
Constance, 2007[17]	ATV 20mg	HDLc mmol/l Measured	219	Mean: 1.25, SD: 0.33	6 weeks	218	NR	Least squares mean % change(SD): 1.63(13.85)	NR
Constance, 2007[17]	SMV 20mg +EZE 10mg	HDLc mmol/l Measured	220	Mean: 1.27, SD: 0.33	6 weeks	219	NR	Least squares mean% change(SD): 2.37(13.85)	p=0.569 Arm 2 vs. Arm 1

Gaudiani, 2005[22]	SMV 40mg	HDLc mmol/l Measured	110	Mean: 1.27 SD: 0.28	24 weeks	107	NR	Least squares mean(SD)% change: 0.3(12.4)	P=0.948
Gaudiani, 2005[22]	SMV 20mg +EZE 10mg	HDLc mmol/l Measured	104	Mean: 1.23 SD: 0.28	24 weeks	103	NR	Least squares mean(SD)% change: 0.2(12.1)	NR
Goldberg, 2006[24] Tomassini, 2009[25] Guyton, 2008[26]	ATV 20mg	Continuous HDLc mg/dL	245	Mean: 46.5	6 weeks	240	NR	% Change from baseline:4.5	Treatment diff, Arm 1 vs. Arm3: 3.4, p:0.001
Goldberg, 2006[24] Tomassini, 2009[25] Guyton, 2008[26]	ATV 40mg	Continuous HDLc mg/dl	245	Mean:46.0	6 weeks	241	NR	% Change from baseline:2.3	NR
Goldberg, 2006[24] Tomassini, 2009[25] Guyton, 2008[26]	SMV 20 + EZE10mg	Continuous HDLc mg/dl	247	Mean: 44.5	6 weeks	238	NR	% Change from baseline: 8.0	NR
Lee, 2013 [33]	EZE/SMV 10/20	Mg/dL	66	Mean: 49.3 SD:11.0	12 weeks	62	Mean: 51.1 SD:11.6	% change= 4.2 SD= 12.7 P<0.05	P=0.184
Lee, 2013 [33]	ATV 20	Mg/dL	66	Mean: 47.8 SD: 10.7	12 weeks	63	Mean: 47.2 SD: 10.5	% change= -0.2 SD= 14.8	NR
<u>Low</u> potency statin combination therapy versus <u>mid</u> potency statin monotherapy									
Kawagoe, 2011[29]	FLV 60mg	HDLc, mg/dl , (All participants have DM)	12	Mean: 55.4 SD: 16	10weeks	12	Mean: 58.1 SD: 18	% Change from baseline: 4.87% (calcuated) p value:0.12	NR

Kawagoe, 2011[29]	FLV 20mg +EZE 10mg	HDLc , mg/dl (All participants have DM)	12	Mean: 57.2 SD: 18	10weeks	12	Mean: 60.5 SD: 20	% Change from baseline: 5.77% (calcuated) p:0.16	p: ns at 10 weeks

ATV atorvastatin; EZE Ezetimibe; FLV Fluvastatin; HDLc high density lipoprotein cholesterol; NR not reported; NS Not significant; SD standard deviation; SE standard error; SMV simvastatin;

Evidence Table E39. Total cholesterol:HDL-c – patients with diabetes mellitus

Author, Year	Arm	Outcome Units	Baseline N	Baseline Outcome	Timepoint (s)	N at Timepoint(s)	Outcomes at Timepoint(s)	Within Arm Comparisons	Between Arm Comparisons
***Mid* potency statin combination therapy versus *high* potency statin monotherapy**									
Constance, 2007[17]	ATV 20mg	TC:HDLc	219	Mean: 3.84, SD: 1.24	6 weeks	218	NR	Least Squares mean % change(SD): -5.90(19.81)	NR
Constance, 2007[17]	SMV 20mg +EZE 10mg	TC:HDLc	220	Mean: 3.65, SD: 0.97	6 weeks	219	NR	Least Squares mean % change(SD): -15.31(19.82)	p≤ 0.001 comparing monotherapy to combination
Gaudiani, 2005[22]	SMV 40mg	TC:HDLc	110	Mean: 3.6, SD: 1.0	24 weeks	107	NR	Least square mean % change(SD): 0.1(17.6)	p<0.001
Gaudiani, 2005[22]	SMV 20mg +EZE 10mg	TC:HDLc	104	Mean: 3.8, SD: 1.2	24 weeks	103	NR	Least square mean% change(SD): -13.4(17.3)	NR

ATV atorvastatin; EZE Ezetimibe; HDLc high density lipoprotein cholesterol; NR not reported; NS Not significant; SD standard deviation; SE standard error; TC total cholesterol

Evidence Table E40. Non-HDL-c – patients with diabetes mellitus

Author, Year	Arm	Outcome Units	Baseline N	Baseline Outcome	Timepoint (s)	N at Timepoint(s)	Outcomes at Timepoint(s)	Within Arm Comparisons	Between Arm Comparisons
***Mid* potency statin combination therapy versus *high* potency statin monotherapy**									
Constance, 2007[17]	ATV 20mg	Non-HDLc Calculated mmol/l	219	Mean: 3.30, SD: 0.88	6 weeks	218	NR	Least squares mean % change(SD): -7.43(24.17)	NR
Constance, 2007[17]	SMV 20mg +EZE10mg	Non-HDLc Calculated mmol/l	220	Mean: 3.18, SD: 0.85	6 weeks	219	NR	Least squares mean% change(SD): -20.91(24.18)	p≤ 0.001 , comparing monotherapy to combination

Gaudiani, 2005[22]	SMV 40mg	Non-HDLc	110	Mean: 3.08, SD: 0.80	24 weeks	107	NR	Least squares mean% change(SD): -1.7(20.7)	-18.3% p<0.001
Gaudiani, 2005[22]	SMV 20mg +EZE10mg	Non-HDLc	104	Mean: 3.8, SD: 1.2	24 weeks	103	NR	Least squares mean% change(SD): -20.0(21.3)	NR
Goldberg, 2006[24] Tomassini, 2009[25] Guyton, 2008[26]	ATV 20mg	Non-HDLc	245	Mean: 184.4	6 weeks	240	NR	% Change from baseline: -41.2	Treatment diff: -6.7 p<0.001, monotherapy to combination
Goldberg, 2006[24] Tomassini, 2009[25] Guyton, 2008[26]	ATV 40mg	Non-HDLc	245	Mean: 184.3	6 weeks	241	NR	% Change from baseline: -46.2	NR
Goldberg, 2006[24] Tomassini, 2009[25] Guyton, 2008[26]	SMV 20mg +EZE10mg	Non-HDLc	247	Mean: 183.3	6 weeks	238	NR	% Change from baseline: -47.9	NR

ATV atorvastatin; EZE Ezetimibe; HDLc high density lipoprotein cholesterol; NR not reported; NS Not significant; SD standard deviation; SE standard error;

Evidence Table E41. Triglycerides – patients with diabetes mellitus

Author, Year	Arm	Outcome Units	Baseline N	Baseline Outcome	Timepoint (s)	N at Timepoint(s)	Outcomes at Timepoint(s)	Within Arm Comparisons	Between Arm Comparisons
<u>Mid</u> potency statin combination therapy versus <u>high</u> potency statin monotherapy									
Bardini, 2010[13]	SMV 40	TG, DM subgroup	50	Mean: 1.6, SD: 0.7	6 weeks	50	%change: -1.8	NR	NR

Bardini, 2010[13]	SMV 20mg +EZE 10mg	TG, DM subgroup	37	Mean: 1.6, SD: 0.7	6 weeks	37	%change: -8.5	NR	NR
Constance, 2007[17]	ATV 20mg	TG mmol/l Measured	219	Median: 1.62, SD: 1.08	6 weeks	218	NR	Least Squares mean %change(SD): -5.46(34.96)	NR
Constance, 2007[17]	SMV 20mg +EZE10mg	TG mmol/l Measured	220	Median: 1.53, SD: 1.01	6 weeks	219	NR	Least Squares mean% change(SD): -9.72(34.39)	p:0.279 comparing monotherapy to combination
Gaudiani, 2005[22]	SMV 40mg	TG	110	Median: 1.71, SD: 1.25	24 weeks	107	NR	Least square median% change(SD): 0.9(31.8)	p:0.291
Gaudiani, 2005[22]	SMV 20mg +EZE 10mg	TG	104	Median: 1.69, SD: 1.30	24 weeks	103	NR	Least square median% change(SD): -3.6(29.7)	NR
Goldberg, 2006[24] Tomassini, 2009[25] Guyton, 2008[26]	ATV 20mg	TGs	245	Mean: 175.0	6 weeks	240	NR	Median % Change from baseline:-26.1	Treatment diff.:-0.5 Comparing monotherapy to combination
Goldberg, 2006[24] Tomassini, 2009[25] Guyton, 2008[26]	ATV 40mg	TGs	245	Mean:175.5	6 weeks	241	NR	Median % Change from baseline: -28.4	NR
Goldberg, 2006[24] Tomassini, 2009[25] Guyton, 2008[26]	SMV 20mg + EZE10mg	TGs	247	Mean: 173.3	6 weeks	238	NR	Median % Change from baseline: -25.7	NR
Lee, 2013 [33]	EZE/SMV 10/20	TGs	66	Mean: 168.8 SD:64.8	12 weeks	62	Mean: 135.3 SD:55.7	% change= -13.4 SD= 37.8 P<0.05	P=0.680

Lee, 2013 [33]	ATV 20	TGs	66	Mean: 174.6 SD: 96.6	12 weeks	63	Mean: 129.6 SD: 55.4	% change= -19.4 SD= 29.2 P<0.05	

ATV atorvastatin; DM diabetes mellitus; EZE Ezetimibe; NR not reported; NS Not significant; SD standard deviation; SE standard error; TG triglyceride

Evidence Table E42. Adherence – patients with diabetes mellitus

Author, Year	Arm	Outcome Units	Baseline N	Baseline Outcome	Timepoint (s)	N at Timepoint(s)	Outcomes at Timepoint(s)	Within Arm Comparisons	Between Arm Comparisons
***Mid* potency statin combination therapy versus *high* potency statin monotherapy**									
Constance, 2007 [17]	ATV 20mg	Treatment adherence	219	NR	6 weeks	219	%=99	NR	NR
Constance, 2007 [17]	SMV 20mg +EZE 10mg	Treatment adherence	220	NR	6 weeks	220	%=98	NR	NR

ATV Atorvastatin; EZE Ezetimibe; NR not reported; SMV simavastatin

Evidence Table E43. Musculoskeletal adverse events – patients with diabetes mellitus

Author, Year	Arm	Outcome Units	Baseline N	Baseline Outcome	Timepoint (s)	N at Timepoint(s)	Outcomes at Timepoint(s)	Within Arm Comparisons	Between Arm Comparisons
***Mid* potency statin combination therapy versus *high* potency statin monotherapy**									
Gaudiani, 2005 [22]	SMV 40mg	CPK greater than 10 times the upper limit of normal	110	NR	24 weeks	110	N=0	NR	NR

Gaudiani, 2005 [22]	SMV 20mg +EZE 10mg	CPK greater than 10 times the upper limit of normal	104	NR	NR	103	N(%)=1(1.0)	NR	NR

EZE Ezetimibe; NR not reported; SMV simavastatin

Evidence Table E44. Myalgia – patients with diabetes mellitus

Author, Year	Arm	Outcome Units	Baseline N	Baseline Outcome	Timepoint (s)	N at Timepoint(s)	Outcomes at Timepoint(s)	Within Arm Comparisons	Between Arm Comparisons
***Mid* potency statin combination therapy versus *high* potency statin monotherapy**									
Constance, 2007 [17]	ATV 20mg	Experiencing myalgia	219	N/A	6 weeks	219	N(%)=0	NR	NR
Constance, 2007 [17]	SMV 20mg +EZE 10mg	Experiencing myalgia	220	N/A	6 weeks	220	N(%)=1(0.5)	NR	NR
Gaudiani, 2005 [22]	SMV 40mg	Experiencing myalgia	110	N/A	24 weeks	110	N=0	NR	NR
Gaudiani, 2005 [22]	SMV 20mg +EZE 10mg	Experiencing myalgia	104	N/A	24 weeks	104	N=0	NR	NR
Lee, 2013 [33]	EZE/SMV 10/20 mg	Events	66	N/A	12 weeks	62	1 (1.6)	NR	NR
Lee, 2013 [33]	ATV 20 mg	Events	66	N/A	12 weeks	63	3 (4.8)	NR	NR

ATV Atorvastatin; EZE Ezetimibe; N/A not applicable; NR not reported; SMV simavastatin

Evidence Table E45. Withdrawal due to adverse events – patients with diabetes mellitus

Author, Year	Arm	Outcome Units	Baseline N	Baseline Outcome	Timepoint (s)	N at Timepoint(s)	Outcomes at Timepoint(s)	Within Arm Comparisons	Between Arm Comparisons
***Mid* potency statin combination therapy versus *high* potency statin monotherapy**									
Bardini, 2010	SMV40 mg	Withdrawal due to adverse events	51	NR	6 weeks	51	Counts: 2, %with events: 4 ,	NR	NR
Bardini, 2010	SMV 20/ EZE10mg	Withdrawal due to adverse events	42	NR	6 weeks	42	Counts: 1, %with events: 2.5 ,	NR	NR
Constance, 2007 [17]	ATV 20mg	Participants withdrawing due to adverse events	219	NR	6 weeks	219	N(%)=2(0.9)	NR	NR
Constance, 2007 [17]	SMV 20mg +EZE 10mg	Participants withdrawing due to adverse events	220	NR	6 weeks	220	N(%)=3(1.4)	NR	NR
Foody, 2010	ATV 20 mg	Withdrawal due to adverse events	258	NR	12 weeks	258	N with events: 3, %with events: 1.2 ,	NR	NR
Foody, 2010	ATV 40mg	Withdrawal due to adverse events	256	NR	12 weeks	256	N with events: 5, %with events: 2 ,	NR	NR
Foody, 2010	SMV 20mg +EZE 10mg	Withdrawal due to adverse events	256	NR	12 weeks	256	N with events: 9, %with events: 3.5 ,	NR	NR
Gaudiani, 2005 [22]	SMV 40mg	Participants withdrawing due to adverse events	110	NR	24 weeks	110	N=5(4.8%)	NR	NR

Gaudiani, 2005 [22]	SMV 20mg +EZE 10mg	Participants withdrawing due to adverse events	104	NR	24 weeks	104	N=2(1.9%)	NR	NR

ATV Atorvastatin; EZE Ezetimibe; NR not reported; SMV simavastatin

Evidence Table E46. Any adverse event – patients with diabetes mellitus

Author, Year	Arm	Outcome Units	Baseline N	Baseline Outcome	Timepoint (s)	N at Timepoint(s)	Outcomes at Timepoint(s)	Within Arm Comparisons	Between Arm Comparisons
***Mid* potency statin combination therapy versus *high* potency statin monotherapy**									
Bardini, 2010[13]	SMV 40mg	At least one adverse event	NR	NR	6 weeks	51	N(%) with events: 10(20),	NR	NR
Bardini, 2010[13]	SMV 20mg EZE10mg	,At least one adverse event	NR	NR	6 weeks	42	N(%) with events: 5(12.5)	NR	p:0.40008 comparing monotherapy to combination
Constance, 2007[17]	ATV 20mg	An adverse event	219	NR	6 weeks	219	N(%):42(19.2)	NR	NR
Constance, 2007[17]	SMV 20mg +EZE 10mg	An adverse event	220	NR	6 weeks	220	N(%):51(23.2)	NR	NR
Foody, 2010[21]	ATV 20mg	At least one adverse event	41	NR	12 weeks	258	N(%) with events: 60(23.3),	NR	NR
Foody, 2010[21]	ATV 40mg	At least one adverse event	31	NR	12 weeks	256	N(%) with events: 67(26.2)	NR	NR
Foody, 2010[21]	SMV 20 +EZE10mg	At least one adverse event	39	NR	12 weeks	256	N(%) with events: 71(27.7)	NR	NR

Gaudiani, 200[22]	SMV 40mg	An adverse event	110	NR	24 weeks	110	N (%)with events:11(10)	NR	NR
Gaudiani, 2005[22]	SMV 20mg +EZE 10mg	An adverse event	104	NR	24 weeks	104	N(%)with events:19(18.3)	NR	NR

ATV Atorvastatin; EZE Ezetimibe; NR not reported; SMV simavastatin

Evidence Table E47. Mortality elderly – elderly patients (> 75 years old)

Author, Year	Arm	Outcome Units	Baseline N	Baseline Outcome	Timepoint (s)	N at Timepoint(s)	Outcomes at Timepoint(s)	Within Arm Comparisons	Between Arm Comparisons
***Mid* potency statin combination therapy versus *high* potency statin monotherapy**									
Zieve, 2010[48] Ben-Yehida, 2011[49]	ATV 20/40mg	All cause mortality elderly,	NR	NR	12 weeks	109	N with events: 0 ,	NR	NR
Zieve, 2010[48] Ben-Yehida, 2011[49]	ATV 10mg + EZE10mg	All cause mortality , elderly	NR	NR	12 weeks	116	N with events: 0 ,	NR	NR

Evidence Table E48. SAE elderly – elderly patients (> 75 years old)

Author, Year	Arm	Outcome Units	Baseline N	Baseline Outcome	Timepoint (s)	N at Timepoint(s)	Outcomes at Timepoint(s)	Within Arm Comparisons	Between Arm Comparisons
***Mid* potency statin combination therapy versus *high* potency statin monotherapy**									
Zieve, 2010[48] Ben-Yehida, 2011[49]	ATV 20/40mg	Serious Adverse Events	NR	NR	12 weeks	109	N(%) with events: 0	NR	NR
Zieve, 2010[48] Ben-Yehida, 2011[49]	ATV 10mg + EZE10mg	Serious Adverse Events	NR	NR	12 weeks	116	N (%)with events: 3 (3)	NR	NR

ATV Atorvastatin; EZE Ezetimibe; NR not reported;

Evidence Table E49. LDL elderly patients (> 75 years old)

Author, Year	Arm	Outcome Units	Baseline N	Baseline Outcome	Timepoint (s)	N at Timepoint (s)	Outcomes at Timepoint(s)	Within Arm Comparisons	Between Arm Comparison
Mid potency statin combination therapy versus high potency statin monotherapy									
Foody, 2010[21]	ATV 20mg	LDLc mg/dl , Elderly, age>=75 yrs	NR	NR	NR	NR	NR	% change from baseline:-47.5, SE: 2	NR
Foody, 2010[21]	ATV 40mg	LDLc mg/dl , ELDERLY	NR	NR	NR	73	NR	% change from baseline:-54, SE:2	NR
Foody, 2010[21]	SMV 20mg +EZE10mg	LDLc mg/dl , Elderly, age>=75 yrs	NR	NR	NR	NR	NR	% change from baseline:-58, SE:2	NR
Zieve, 2010[48] Ben-Yehida, 2011[49]	ATV 20mg/40mg	LDLc , mg/dl, Measured, ELDERLY	109	Mean: 2.5, SD: 0.48	12 weeks	106	LCL 95%: -24.8 , HCL 95%: -15.7, Least squares mean % change:-20.2	NR	NR
Zieve, 2010[48] Ben-Yehida, 2011[49]	ATV10mg +EZE10mg	LDLc mg/dl Measured Elderly	116	Mean: 2.78, SD: 1.12	12 weeks	111	LCL 95%: -25.1 , HCL 95%: -16.0 , Least squares mean % change:-20.6	NR	95%LCL: -6.5, 95%HCL: 5.7, Treatment Diff: -0.4, comparing monotherapy to combination at 12 weeks

ATV atorvastatin; EZE Ezetimibe; HCL higher confidence limit; IQR interquartile range; LCL lower confidence limit; LDLc low density lipoprotein cholesterol; NR not reported; NS Not significant; SD standard deviation; SE standard error; SMV simvastatin;

Evidence Table E50. HDL-c – elderly

Author, Year	Arm	Outcome Units	Baseline N	Baseline Outcome	Timepoint (s)	N at Timepoint(s)	Outcomes at Timepoint(s)	Within Arm Comparisons	Between Arm Comparisons
***Mid* potency statin combination therapy versus *high* potency statin monotherapy**									
Zieve, 2010[48] Ben-Yehida, 2011[49]	ATV 20mg/40mg	HDLc, mg/dl Calculated ELDERLY	109	Mean: 1.39, SD: 0.29	12weeks	106	LCL 95%: -4.1 , HCL 95%: 1.3 , Least square mean %change: -1.4	NR	NR
Zieve, 2010[48] Ben-Yehida, 2011[49]	ATV 10mg + EZE10mg	HDLc mg/dl Calculated ELDERLY	116	Mean: 1.43, SD: 0.37	12weeks	111	LCL 95%: -0.2 , HCL 95%: -5.0 , Least squares mean % change: 2.4	NR	95%LCL: 0.2, 95%HCL: 7.3, Treatment Diff: 3.8, comparing monotherapy to combination at 12 weeks

ATV atorvastatin; EZE Ezetimibe; HCL higher confidence limit; HDLc high density lipoprotein cholesterol; LCL lower confidence limit; NR not reported; SD standard deviation;

Evidence Table E51. Total cholesterol:HDL – elderly patients

Author, Year	Arm	Outcome Units	Baseline N	Baseline Outcome	Timepoint (s)	N at Timepoint(s)	Outcomes at Timepoint(s)	Within Arm Comparisons	Between Arm Comparisons
***Mid* potency statin combination therapy versus *high* potency statin monotherapy**									
Zieve, 2010[48] Ben-Yehida, 2011[49]	ATV 20/40 mg	TC:HDLc , Elderly	109	Mean: 3.4, SD: 0.7	12 weeks	106	LCL 95%: -14.3, HCL 95%: -7.3 , Least Squares mean % change: -10.8	NR	NR

Zieve, 2010[48] Ben-Yehida, 2011[49]	ATV10mg + EZE 10mg	TC:HDLc , Elderly	116	Mean: 3.6, SD: 1.3	12 weeks	111	LCL 95%: -17.7, HCL 95%: -10.8, Least Squares mean % change: -14.2	NR	95%LCL: -8.1, 95%HCL: 1.2, Treatment Diff: -3.5 comparing monotherapy to combination

ATV atorvastatin; EZE Ezetimibe; HCL higher confidence limit; HDLc high density lipoprotein cholesterol; LCL lower confidence limit; NR not reported; SD standard deviation;

Evidence Table E52. Any adverse event – elderly patients

Author, Year	Arm	Outcome Units	Baseline N	Baseline Outcome	Timepoint (s)	N at Timepoint(s)	Outcomes at Timepoint(s)	Within Arm Comparisons	Between Arm Comparisons
***Mid* potency statin combination therapy versus *high* potency statin monotherapy**									
Zieve, 2010[48] Ben-Yehida, 2011[49]	ATV 20/40mg	At least one adverse event, Elderly	109	NR	12 weeks	109	N(%) with events: 34(31),	NR	NR
Zieve, 2010[48] Ben-Yehida, 2011[49]	ATV 10mg + EZE10mg	At least one adverse event, Elderly	106	NR	12 weeks	116	N(%) with events: 35(30),	NR	NR

ATV atorvastatin; EZE Ezetimibe; NR not reported;

Evidence Table E53. Withdrawal due to adverse events – elderly patients

Author, Year	Arm	Outcome Units	Baseline N	Baseline Outcome	Timepoint (s)	N at Timepoint(s)	Outcomes at Timepoint(s)	Within Arm Comparisons	Between Arm Comparisons
***Mid** potency statin combination therapy versus **high** potency statin monotherapy*									
Zieve, 2010[48] Ben-Yehida, 2011[49]	ATV 20/40mg	Withdrawal due to adverse events , elderly	109	NR	12 weeks	109	%: 2, N with events: 2 ,	NR	NR
Zieve, 2010[48] Ben-Yehida, 2011[49]	ATV 10mg + EZE 10mg	Withdrawal due to adverse events , elderly	116	NR	12 weeks	116	%: 6 N with events: 7 ,	NR	NR

ATV atorvastatin; EZE Ezetimibe; NR not reported;

Evidence Table E54. Elevated liver transaminases – elderly patients

Author, Year	Arm	Outcome Units	Baseline N	Baseline Outcome	Timepoint (s)	N at Timepoint(s)	Outcomes at Timepoint(s)	Within Arm Comparisons	Between Arm Comparisons
***Mid** potency statin combination therapy versus **high** potency statin monotherapy*									
Zieve, 2010[48] Ben-Yehida, 2011[49]	ATV 20/40 mg	Elevated AST and/or ALT > 3x ULN and/or hepatitis, Elderly	109	NR	12 weeks	108	N with events: 0	NR	NR
Zieve, 2010[48] Ben-Yehida, 2011[49]	ATV 10mg + EZE10mg	Elevated AST and/or ALT > 3x ULN and/or hepatitis, Elderly	116	NR	12 weeks	115	N with events: 0	NR	NR

ALT alanine transaminase; AST aspartate transaminase; ATV atorvastatin; EZE Ezetimibe; NR not reported; ULN upper normal limit

Evidence Table E55. Musculoskeletal adverse events – elderly

Author, Year	Arm	Outcome Units	Baseline N	Baseline Outcome	Timepoint (s)	N at Timepoint(s)	Outcomes at Timepoint(s)	Within Arm Comparisons	Between Arm Compariso ns
***Mid* potency statin combination therapy versus *high* potency statin monotherapy**									
Zieve, 2010[48] Ben-Yehida, 2011[49]	ATV 20/40 mg	Participants with CPK above 10 times the upper limit of normal , of normal Elderly	109	NR	12 weeks	108	N with events: 0 ,	NR	NR
Zieve, 2010[48] Ben-Yehida, 2011[49]	ATV 10mg + EZE 10mg	Participants with CPK above 10 times the upper limit of normal , elderly	116	NR	12 weeks	115	N with events: 0 ,	NR	NR

ATV atorvastatin; EZE Ezetimibe; NR not reported;

Evidence Table E56. LDL-c – female patients

Author, Year	Arm	Outcome Units	Baseline N	Baseline Outcome	Timepoint (s)	N at Timepoint (s)	Outcomes at Timepoint(s)	Within Arm Comparisons	Between Arm Comparison
***Mid* potency statin combination therapy versus *high* potency statin monotherapy**									
Foody, 2010[21]	ATV 20mg	LDLc mg/dl , FEMALES	NR	NR	NR	NR	NR	% change from baseline: -46, SE:2	NR
Foody, 2010[21]	ATV 40mg	LDLc mg/dl , FEMALES	NR	NR	NR	149	NR	% change from baseline:-50, SE:1	NR
Foody, 2010[21]	SMV 20mg +EZE10mg	LDLc mg/dl ,	NR	NR	NR	NR	NR	% change from baseline:-54,	NR

Author, Year	Arm	Outcome Units	Baseline N	Baseline Outcome	Timepoint (s)	N at Timepoint (s)	Outcomes at Timepoint(s)	Within Arm Comparisons	Between Arm Comparison
		FEMALES						SE:2	
Gaudiani, 2005[22]	SMV 40mg	LDL-c (FEMALES) mmol/l-	NR	NR	24 weeks	48	NR	NR	Least square mean %change(95%CI): -18(-8,-30)
Gaudiani, 2005[22]	SMV 20mg +EZE 10mg	LDL-c (FEMALES) mmol/l	NR	NR	24 weeks	42	NR	NR	NR
Zieve, 2010[48] Ben-Yehida, 2011[49]	ATV 20mg/40mg	LDLc mg/dl , Measured Female	286	NR	12 weeks	270	SE: 2, % change from baseline: -17,	NR	NR
Zieve, 2010[48] Ben-Yehida, 2011[49]	ATV10mg +EZE10mg	LDLc mg/dl , Measured Female	277	NR	12 weeks	275	SE: 2 , ,% change from baseline: -21,	NR	NR

ATV Atorvastatin; CI confidence intervals; EZE ezetimibe; LDLc low density lipoprotein cholesterol; NR not reported; SD standard deviation; SE standard error; SMV Simvastatin;

Evidence Table E57. LDL – Asian patients

Author, Year	Arm	Outcome Units	Baseline N	Baseline Outcome	Timepoint (s)	N at Timepoint (s)	Outcomes at Timepoint(s)	Within Arm Comparisons	Between Arm Comparison
***Mid** potency statin combination therapy versus **high** potency statin monotherapy*									
Foody, 2010[21]	ATV 20mg	LDLc mg/dl : ASIAN RACE	NR	NR	NR	NR	NR	% change from baseline:-50, SE:5	NR
Foody, 2010[21]	ATV 40mg	LDLc mg/dl , ASIAN RACE	NR	NR	NR	10	NR	% change from baseline:-48, SE:3	NR

Author, Year	Arm	Outcome Units	Baseline N	Baseline Outcome	Timepoint (s)	N at Timepoint (s)	Outcomes at Timepoint(s)	Within Arm Comparisons	Between Arm Comparison
Foody, 2010[21]	SMV 20mg +EZE10mg	LDLc mg/dl , ASIAN RACE	NR	NR	NR	NR	NR	% change from baseline:-42, SE:2	NR

ATV Atorvastatin; CI confidence intervals; EZE ezetimibe; LDLc low density lipoprotein cholesterol; NR not reported; SD standard deviation; SE standard error; SMV Simvastatin;

Evidence Table E58. LDL – Black patients

Author, Year	Arm	Outcome Units	Baseline N	Baseline Outcome	Timepoint (s)	N at Timepoint (s)	Outcomes at Timepoint(s)	Within Arm Comparisons	Between Arm Comparison
***Mid* potency statin combination therapy versus *high* potency statin monotherapy**									
Foody, 2010[21]	ATV 20mg	LDLc mg/dl , BLACK RACE	NR	NR	NR	NR	NR	% change from baseline:-50, SE:6	NR
Foody, 2010[21]	ATV 40mg	LDLc mg/dl , BLACK RACE	NR	NR	NR	9		% change from baseline:-49, SE:6	NR
Foody, 2010[21]	SMV 20mg +EZE10mg	LDLc mg/dl , BLACK RACE	NR	NR	NR	NR	NR	% change from baseline:-65, SE:10	NR
Gaudiani, 2005[22]	SMV 40mg	LDL-c BLACK RACE mmol/l	NR	NR	24 weeks	12	NR	NR	Least square mean %change(95%CI): -15(0,-30)
Gaudiani, 2005[22]	SMV 20mg +EZE 10mg	LDL-c BLACK RACE mmol/l	NR	NR	24 weeks	16	NR	NR	NR

ATV Atorvastatin; CI confidence intervals; EZE ezetimibe; LDLc low density lipoprotein cholesterol; NR not reported; SD standard deviation; SE standard error; SMV Simvastatin;

Evidence Table E59. LDL – Hispanic patients

Author, Year	Arm	Outcome Units	Baseline N	Baseline Outcome	Timepoint (s)	N at Timepoint (s)	Outcomes at Timepoint(s)	Within Arm Comparisons	Between Arm Comparison
***Mid** potency statin combination therapy versus **high** potency statin monotherapy*									
Gaudiani, 2005 [22]	SMV 40mg	LDL-c HISPANIC mmol/l	NR	NR	24 weeks	28	NR	NR	Least square mean %change(95%CI): -26(-15,-38)
Gaudiani, 2005 [22]	SMV 20mg +EZE 10mg	LDL-c HISPANIC mmol/l	NR	NR	24 weeks	24	NR	NR	NR

CI confidence intervals; EZE ezetimibe; LDLc low density lipoprotein cholesterol; NR not reported; SD standard deviation; SE standard error; SMV Simvastatin;

Evidence Table E60. Summary of evidence available for subgroups comparing combination therapy with ezetimibe and statin to intensification of statin monotherapy

		Subgroup						
Outcomes	**Potency comparison**	**CHD # trials (#participants)**	**Diabetes mellitus # trials (#participants)**	**Females # trials (#participants)**	**Asian # trials (#participants)**	**Black # trials (#participants)**	**Hispanic # trials (#participants)**	**Elderly # trials (#participants)**
LDL-c	Mid potency combination therapy vs high potency monotherapy	12 trials* (1233)	8 trials* 1597	2 trials* (547)	1 trial (NR)	2 trials* (28)	1 trial (52)	2 trials* (225)
	Low potency combination therapy vs high potency monotherapy		1 trial 21					
	Low potency combination therapy vs mid potency monotherapy		1 trial 24					
HDL-c	Mid potency combination therapy vs high potency monotherapy	11 trials* (1105)	5 trials 1578					1 trial (217)
	Low potency combination therapy vs high potency monotherapy		1 trial 21					
	Low potency combination therapy vs mid potency monotherapy		1 trial 24					
Non-HDL-c	Mid potency combination therapy vs high potency monotherapy		3 trials (1366)					
	Low potency combination							

		Subgroup						
Outcomes	**Potency comparison**	**CHD # trials (#participants)**	**Diabetes mellitus # trials (#participants)**	**Females # trials (#participants)**	**Asian # trials (#participants)**	**Black # trials (#participants)**	**Hispanic # trials (#participants)**	**Elderly # trials (#participants)**
	therapy vs high potency monotherapy							
	Low potency combination therapy vs mid potency monotherapy							
Triglycerides	Mid potency combination therapy vs high potency monotherapy		5 trials (1578)					
	Low potency combination therapy vs high potency monotherapy							
	Low potency combination therapy vs mid potency monotherapy							
Total Cholesterol:HDL	Mid potency combination therapy vs high potency monotherapy	1 trial (422)	2 trials (647)					1 trial (218)
	Low potency combination therapy vs high potency monotherapy							
	Low potency combination therapy vs mid potency monotherapy							
LDL target	Mid potency	4 trials	3 trials					1 trial

		Subgroup						
Outcomes	**Potency comparison**	**CHD # trials (#participants)**	**Diabetes mellitus # trials (#participants)**	**Females # trials (#participants)**	**Asian # trials (#participants)**	**Black # trials (#participants)**	**Hispanic # trials (#participants)**	**Elderly # trials (#participants)**
attainment	combination therapy vs high potency monotherapy	(889)	(1246)					(218)
	Low potency combination therapy vs high potency monotherapy							
	Low potency combination therapy vs mid potency monotherapy							
Adherence	Mid potency combination therapy vs high potency monotherapy	2 trials* (93)	1 trial (439)					
	Low potency combination therapy vs high potency monotherapy							
	Low potency combination therapy vs mid potency monotherapy							
Any adverse event	Mid potency combination therapy vs high potency monotherapy	3 trials (632)	4 trials (1416)					1trial (225)
	Low potency combination therapy vs high potency monotherapy							

		Subgroup						
Outcomes	**Potency comparison**	**CHD # trials (#participants)**	**Diabetes mellitus # trials (#participants)**	**Females # trials (#participants)**	**Asian # trials (#participants)**	**Black # trials (#participants)**	**Hispanic # trials (#participants)**	**Elderly # trials (#participants)**
	Low potency combination therapy vs mid potency monotherapy							
Withdrawal due to adverse events	Mid potency combination therapy vs high potency monotherapy	5 trials* (632)	4 trials (1516)					1trial (225)
	Low potency combination therapy vs high potency monotherapy							
	Low potency combination therapy vs mid potency monotherapy							
Serious adverse events	Mid potency combination therapy vs high potency monotherapy	3 trials (632)	5 trials (1641)					1trial (225)
	Low potency combination therapy vs high potency monotherapy							
	Low potency combination therapy vs mid potency monotherapy							
Mortality	Mid potency combination therapy vs high potency	1 trial*	2 trials (806)					1trial (225)

		Subgroup						
Outcomes	**Potency comparison**	**CHD # trials (#participants)**	**Diabetes mellitus # trials (#participants)**	**Females # trials (#participants)**	**Asian # trials (#participants)**	**Black # trials (#participants)**	**Hispanic # trials (#participants)**	**Elderly # trials (#participants)**
	monotherapy							
	Low potency combination therapy vs high potency monotherapy							
	Low potency combination therapy vs mid potency monotherapy							
Elevated liver transaminases	Mid potency combination therapy vs high potency monotherapy	6 trials* (713)						1 trial (225)
	Low potency combination therapy vs high potency monotherapy							
	Low potency combination therapy vs mid potency monotherapy							
Elevated CPK	Mid potency combination therapy vs high potency monotherapy	4 trials* (632)	1 trial (213)					1 trial (225)
	Low potency combination therapy vs high potency monotherapy							
	Low potency combination therapy vs							

		Subgroup						
Outcomes	**Potency comparison**	**CHD # trials (#participants)**	**Diabetes mellitus # trials (#participants)**	**Females # trials (#participants)**	**Asian # trials (#participants)**	**Black # trials (#participants)**	**Hispanic # trials (#participants)**	**Elderly # trials (#participants)**
	mid potency monotherapy							
Myalgia	Mid potency combination therapy vs high potency monotherapy	1 trial (78)	3 trials (778)					
	Low potency combination therapy vs high potency monotherapy							
	Low potency combination therapy vs mid potency monotherapy							

H v M= high potency monotherapy versus mid potency combination therapy; H v L= high potency monotherapy versus low potency combination therapy; M v L= mid potency monotherapy versus low potency combination therapy; CPK= creatinine phosphokinase; HDL= high density lipoprotein; LDL= low density lipoprotein

*means at least one of the trials did not report the number of participants, blank cell means no trial

Evidence Table E61. Study quality assessment – ezetimibe

Author, Year	2009 CER Jadad Score	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14
Ahmed, 2008[8]	NA	U	U	U	H	L	H	H	N	Y	U	U	U	Y	N
Araujo, 2010[9]	NA	U	U	U	U	U	U	U	N	Y	U	U	U	Y	N
Averna, 2010[10]	NA	L	L	L	L	L	L	L	N	N	Y	Y	Y	Y	N
Ballantyne 2003[11]	2	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Ballantyne, 2004[12]	2	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Bardini, 2010[13]	NA	L	U	L	L	L	L	L	N	Y	U	U	Y	Y	N
Barrios, 2005[14]	3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Bays, 2004	5	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Catapano, 2006[15]	3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Cho, 2011[16]	NA	L	U	H	H	L	L	L	N	Y	Y	Y	Y	Y	N
Constance, 2007[17]	3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Davidson, 2002[18]	4	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Feldman, 2004[19]	2	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Florentin, 2011[20]	NA	L	U	H	H	H	L	L	N	Y	Y	Y	Y	Y	N
Foody, 2010[21]	NA	L	L	L	L	L	L	L	N	Y	Y	Y	Y	Y	N
Gaudiani, 2005[22]	3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Goldberg, 2004[23]	5	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Goldberg, 2006[24] Guyton, 2008[26] Tomassini, 2009[25]	3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Hamdan, 2011[27]	NA	U	U	L	L	L	L	L	N	Y	Y	Y	Y	Y	N
Her, 2010[28]	NA	H	H	H	H	H	L	L	L	L	L	L	L	L	L
Kawagoe, 2011[29]	NA	H	H	H	H	L	L	L	N	U	U	U	U	Y	N
Kerzner, 2003[30]	3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Lee, 2011[31]	NA	U	U	H	H	L	L	L	N	U	Y	Y	Y	Y	N
Lee, 2012[32]	NA	U	U	H	H	U	L	L	N	Y	Y	Y	Y	Y	N
Lee, 2013[33]	NA	L	H	H	H	H	L	L	L	L	L	L	L	L	L
Liberopoulos, 2013[34]	NA	L	H	L	H	L	L	L	N	Y	Y	U	Y	Y	N
Matsue, 2013[35]	NA	L	H	H	H	H	L	L	L	L	L	L	L	L	L
McKenney, 2007[36]	2	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Moutzouri, 2011[37]	NA	L	L	L	H	L	L	L	N	U	Y	Y	Y	Y	N
Moutzouri, 2012[38]	NA	L	U	H	H	U	L	L	N	Y	Y	Y	Y	Y	N
Okada, 2011[39]	NA	H	U	H	U	U	L	L	N	U	Y	U	U	Y	N
Pesaro, 2012[41]	NA	U	U	L	L	L	L	L	N	Y	U	U	U	Y	N
Piorkowski, 2007[42]	1	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Robinson, 2009[43]	NA	L	L	L	L	L	U	U	N	N	Y	Y	Y	Y	N
Roeters van Lennep, H.W.O, 2007[44]	3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Rudofsky, 2012[45]	NA	L	L	L	L	L	L	L	N	Y	Y	U	U	Y	N
Stein, 2004[46]	3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Yamazaki, 2013[47]	NA	U	L	H	H	H	L	L	N	Y	Y	Y	Y	Y	N

Zieve, 2010[48] Ben-Yehida, 2011[49]	NA	L	L	L	L	L	L	L	N	N	Y	Y	U	Y	N

CER comparative effectiveness report; H high; L low; N no; NA not applicable; U unclear or unsure.

Q1. What is the risk of selection bias (biased allocation to interventions) due to inadequate generation of a randomized sequence?
Q2. What is the risk of selection bias (biased allocation to interventions) due to inadequate concealment of allocations before assignment?
Q3. For each main outcome or class of outcomes, what is the risk of performance bias due to knowledge of the allocated interventions by participants and personnel during the study (lack of study participant and personnel blinding)?
Q4. Was the care provider blinded to the intervention?
Q5. For each main outcome or class of outcomes, what is the risk of detection bias due to knowledge of the allocated interventions by outcome assessment (lack of outcome assessor blinding)?
Q6. For each main outcome or class of outcomes, what is the risk of attrition bias due to amount, nature, or handling of incomplete outcome data?
Q7. What is the risk of reporting bias due to selective outcome reporting?
Q8. Are there other biases due to problems not covered in 1-6?
Q9. Were all randomized participants analyzed in the group to which they were allocated?
Q10. Were the groups similar at baseline regarding the most important prognostic indicators?
Q11. Were co-interventions avoided or similar?
Q12. Was the compliance acceptable in all groups?
Q13. Was the timing of the outcome assessment similar in all groups?
Q14. Are there other risks of bias?

Evidence Table E62. Study characteristics – fibrates

Author, Year Trial #, "Acronym"	Study Design Site(s)	Inclusion Criteria	Participant Use of Lipid-Modifying Agents Prior to Trial	Treatment Duration Washout Period Run-In Period	Arms (Potency)	Subgroup Analyses	Pharmaceutical Industry Support Conflict of Interest disclosure by author
Athyros, 2002 [51]	Parallel Arm RCT Single center Europe	Patients with familial combined hyperlipidemia, patients were considered to have this lipid disorder, after exclusion of secondary dyslipidemias, on clinical and biochemical criteria: family history of dyslipidaemia IIa, IIb or IV and/or premature CAD, total cholesterol >250 mg/dl, TG> 200 mg/dl and <400 mg/dl, HDL <40 mg/dl, and apolipoprotein (apo) B >150 mg/dl, at baseline while off therapy. In all patients, liver dysfunction was excluded and normal renal function was established.	Discontinued 6 weeks before trial	12 months 6 weeks 6-week dietary run-in	Arm1: (H) ATV 20mg Arm 2: (L) PRV 20mg + Gemfibrosil 1200mg Arm 3: (M) SMV 20mg + Gemfibrosil 1200mg Arm4: (M) SMV 20mg + Ciprofibrate 100mg Arm5: (L) PRV 20mg + Ciprofibrate 100mg	None	NR NR
Farnier, 2011 [52]	Parallel arm RCT Multicenter Europe	Patients ≥18 years with type 2 diabetes and mixed hyperlipidemia (total cholesterol >200 mg/dL, TG >150 mg/dL, After the active-treatment run-in period, eligible patients with a non–HDL-C concentration >=130 mg/dL or a LDL-C concentration >=100 mg/dL and a fasting TG concentration >=150 and <=600 mg/dL 1 week before the randomization visit (week 0) were randomly assigned to either FDC or simvastatin 20 mg for 12 weeks., no uncontrolled	Discontinued 6 weeks before trial	12-Weeks NA 12-week dietary run-in and 6-week run-in of SMV 20mg daily	Arm 1: (M) SMV 20mg Arm 2: (L) PRV 40mg + Fenofibrate 160mg	Overall population represents subgroup of interest: Diabetics	Yes, Financial relationship with pharmaceuticals Yes, Employee of pharmaceutical company

Author, Year Trial #, "Acronym"	Study Design Site(s)	Inclusion Criteria	Participant Use of Lipid-Modifying Agents Prior to Trial	Treatment Duration Washout Period Run-In Period	Arms (Potency)	Subgroup Analyses	Pharmaceutical Industry Support Conflict of Interest disclosure by author
		diabetes (HbA1c>8.5% 1 week before randomization) and type 2 diabetes requiring insulin No known cardiovascular disease, type I, IIa, IV, or V hyperlipidemia; history sensitivity or allergy to statins and/or fibric acid derivatives; uncontrolled hypertension; history of malignancy; personal or family history of hereditary muscle disease; uncontrolled hypothyroidism; abnormal liver function; creatine phosphokinase>3 x ULN; creatinine clearance 15 mg/L; use of prohibited concomitant medications; pregnancy or breastfeeding; nonadherence to the NCEP ATP III standardized diet; high alcohol consumption or diabetes requiring insulin					
Mohiuddin, 2009 [53]	Parallel arm RCT Multicenter North America	Patients >18yrs with mixed dyslipidemia: -HDL-C <40mg/dl(men) or <50mg/dl(women) -TGs>or=150mg/dl -LDL-C >or=130mg/dl No type 1 diabetes mellitus or uncontrolled type 2 diabetes mellitus, no history of diabetic ketoacidosis	Yes-Prior to trial entry	12 weeks No 6 weeks	Arm 1: (H) SMV 40mg Arm 2: (H) SMV 80mg Arm 3: (M) SMV 20mg + Fenofibric acid 135mg	No subgroup analyses were conducted	Yes, Financial relationship with pharmaceuticals Yes

Author, Year Trial #, "Acronym"	Study Design Site(s)	Inclusion Criteria	Participant Use of Lipid-Modifying Agents Prior to Trial	Treatment Duration Washout Period Run-In Period	Arms (Potency)	Subgroup Analyses	Pharmaceutical Industry Support Conflict of Interest disclosure by author
Shah, 2007[54]	Parallel arm RCT Single Center Asia	Patients with acute coronary syndrome (ACS) who had undergone a percutaneous transluminal coronary angioplasty procedure (at time of eNot reportedollment) Other 1 inclusion criteria: Patients without: second- or third-degree atrioventricular block, renal or hepatic failure, recent cerebrovascular events, valve replacement surgery or balloon mitral valvuloplasty, taking non-statin antilipid medication	NR	3-Months NA NR	Arm 1: (H) ATV 20mg daily Arm 2: (H) SMV 40mg daily Arm 3: (M) ATV 10mg + Fenofibrate 200 mg Arm 4: (M) SMV 20mg + Fenofibrate 200mg	Overall population represents subgroup of interest: Pre-existing CHD	NR NR

RCT= randomized controlled trial; NA= not applicable; NR not reported

Evidence Table E63. Baseline population characteristics – fibrates

Author, Year	Arms	N	Age	Female N (%)	Race N (%)	Smoking Status N (%)	Prior Stroke N (%)	Prior MI N (%)	Prior Revascu-larization N (%)	Diabetic Patients N (%)	LDL in mg/dL	Between Group Differences
Athyros, 2002 [51]	Arm1: (H) ATV 20mg Arm 2: (L) PRV 20mg + Gemfibrosil 1200mg Arm 3: (M) SMV 20mg + Gemfibrosil 1200mg Arm4: (M) SMV 20mg + Ciprofibrate 100mg Arm5: (L) PRV 20mg + Ciprofibrate 100mg	Arm 1 131 Arm 2 133 Arm 3 129 Arm 4 129 Arm 5 132	Arm 1 Median: 52 Range: 36-65 Arm 2 Median: 50 Range: 32-67 Arm 3 Median: 50 Range: 31-65 Arm 4 Median: 50 Range: 34-63 Arm 5 Median: 51 Range: 35-62	Arm 1: 38 (29) Arm 2: 36 (27) Arm 3: 34 (26) Arm 4: 39 (30) Arm 5: 43 (33)	NR	NR	Arm 1 56 Arm 2 55 Arm 3 53 Arm 4 56 Arm 5 57	NR	NR	NR	Arm 1 Mean: 203 SD: 13 Arm 2 Mean: 208 SD: 15 Arm 3 Mean: 199 SD: 16 Arm 4 Mean: 196 SD: 15 Arm 5 Mean: 203 SD: 17	NR
Farnier, 2011 [52]	Arm 1: (M) SMV 20mg Arm 2: (L) PRV 40mg + Fenofibrate 160mg	Arm 1 146 Arm 2 145	Arm 1 Mean: 57.2 SD: 9.5 Arm 2 Mean: 56.1 SD: 8.3	Arm 1 72 (49) Arm 2 79 (55)	NR	NR	NR	NR	NR	Arm 1 146 (100) Arm 2 145 (100)	Arm 1 Mean: 127.6 SD: 29.8 Arm 2 Mean: 126.9 SD: 28.8	NR
Mohiuddin, 2009 [53]	Arm 1: (H) SMV 40mg	Arm 1: 116	Arm 1 Mean: 53.7 Range: 33-	NR	Arm1: White: 112 (97)	NR	NR	NR	NR	NR	NR	NR

Author, Year	Arms	N	Age	Female N (%)	Race N (%)	Smoking Status N (%)	Prior Stroke N (%)	Prior MI N (%)	Prior Revascu-larization N (%)	Diabetic Patients N (%)	LDL in mg/dL	Between Group Differences
	Arm 2: (H) SMV 80mg Arm 3: (M) SMV 20mg + Fenofibric acid 135mg	Arm 2: 59 Arm 3: 119	77 Arm 2 Mean: 55.8 Range: 30-80 Arm 3 Mean: 55.9 Range: 25-82		Black: 2 (2) Native American: 2 (2) Arm2: White: 55 (93) Black: 1 (2) Asian: 1 (2) Arm3: White: 108 (91) Black: 4 (3) Native American: 1 (1) Asian: 4 (3)							
Shah, 2007[54]	Arm 1: (H) ATV 20mg daily Arm 2: (H) SMV 40mg daily Arm 3: (M) ATV 10mg + Fenofibrate 200 mg Arm 4: (M) SMV 20mg + Fenofibrate 200mg	Arm 1 25 Arm 2 27 Arm 3 25 Arm 4 25	Arm 1 Mean: 56.8 SD: 9.4 Arm 2 Mean: 58.4 SD: 11.4 Arm 3 Mean: 56.4 SD: 10.0 Arm 4 Mean: 58.4 SD: 11.4	Arm 1 N: 1 (4) Arm 2 N: 2 (7.4) Arm 3 N: 3 (12) Arm 4 N: 5 (20)	NR	Arm 1 Current: 3 (12) Arm 2 Current: 4 (15) Arm 3 Current: 5 (20) Arm 4 Current: 2 (8)	NR	Arm 1 25 (100) Arm 2 27 (100) Arm 3 25 (100) Arm 4 25 (100)	Arm 1 25 (100) Arm 2 27 (100) Arm 3 25 (100) Arm 4 25 (100)	Arm 1 6 (24) Arm 2 8 (30) Arm 3 9 (36) Arm 4 12 (48)	Arm 1 Mean: 100.5 SD: 34.8 Arm 2 Mean: 92.8 SD: 23.2 Arm 3 Mean: 92.8 SD: 34.8 Arm 4 Mean: 92.8 SD: 23.2	NR

MI myocardial infarction; SD standard deviation; NR not reported

*Arms not eligible for our review

Evidence Table E64. Mortality – fibrates

Author, Year	Group	Baseline N	Baseline outcome	Follow up timing	N at follow up	N with event at follow up	Between group difference
Farnier, 2011 [52]	Arm 1: (M) SMV 20mg	NR	NR	12 weeks	146	0	
	Arm 2: (L) PRV 40mg + Fenofibrate 160mg	NR	NR	12 weeks	145	0	NR

Evidence Table E65. Unspecified myocardial infarction (MI) – fibrates

Author, Year	Group	Baseline N	Baseline outcome	Follow up timing	N at follow up	N with event at follow up	Between group difference
Farnier, 2011 [52]	Arm 1: (M) SMV 20mg	NR	NR	12 weeks	146	0	
	Arm 2: (L) PRV 40mg + Fenofibrate 160mg	NR	NR	12 weeks	145	1	NR

Evidence Table E66. Transient ischemic attack (TIA) – fibrates

Author, Year	Group	Baseline N	Baseline outcome	Follow up timing	N at follow up	N with event at follow up	Between group difference
Farnier, 2011 [52]	Arm 1: (M) SMV 20mg	NR	NR	12 weeks	146	1	
	Arm 2: (L) PRV 40mg + Fenofibrate 160mg	NR	NR	12 weeks	145	0	NR

Evidence Table E67. Serious adverse events (SAE) – fibrates

Author, Year	Group	Baseline N	Baseline outcome	Follow up timing	N at follow up	N (%)with event at follow up	Between group difference
Farnier, 2011 [52]	Arm 1: (M) SMV 20mg	NR	NR	12weeks	146	1 (0.7)	
	Arm 2: (L) PRV 40mg + Fenofibrate 160mg	NR	NR	12weeks	145	1 (0.7)	NR

Evidence Table E68. LDL (mg/dL) outcome – fibrates

Author, Year	Group	Baseline N	Baseline outcome	Follow up timing	N at follow up	Outcome at follow up	Within group differences	Between group difference
Athyros, 2002 [51]	Arm1: (H) ATV 20mg	131	Mean: 203 SD: 13	12 months	131	NR	Mean % change: (-46)	
	Arm 2: (L) PRV 20mg + Gemfibrosil 1200mg	133	Mean: 208 SD: 15	12 months	133	NR	Mean % change: (-35)	Arm1 vs Arm2: Difference= 25, 95% CI= 22-28, p=0.0001
	Arm 3: (M) SMV 20mg + Gemfibrosil 1200mg	129	Mean: 199 SD: 16	12 months	129	NR	Mean % change: (-38)	Arm1 vs Arm3: Difference=11, 95% CI= 8-13, p=0.0008
	Arm4: (M) SMV 20mg + Ciprofibrate 100mg	129	Mean: 196 SD: 15	12 months	129	NR	Mean % change: (-41)	Arm1 vs Arm4: Difference=7, 95% CI= 5-11, p=0.003
	Arm5: (L) PRV 20mg + Ciprofibrate 100mg	132	Mean: 203 SD: 17	12 months	132	NR	Mean % change: (-40)	Arm1 vs Arm5: Difference= 12, 95% CI= 9-15, p=0.0005
Farnier, 2011 [52]	Arm 1: (M) SMV 20mg	144	Mean: 127.6 SD: 29.8	12 weeks	144	Mean: 117.2 SD: 32.7	Mean % change: (-6.8) SE: 1.9 p<0.001	
	Arm 2: (L) PRV 40mg + Fenofibrate 160mg	145	Mean: 126.9 SD: 28.8	12 weeks	145	Mean: 117.3 SD: 33.5	Mean % change:(-5.3) SE: 1.9 p=0.016	Difference=+1.4 p=0.29
Mohiuddin, 2009 [53]	Arm 1: (H) SMV 40mg	106	Mean: 163.3	12 weeks	NR	Mean: 108.1	Mean %change:(-31.7) SE: 2.0	
	Arm 2: (H) SMV 80mg	55	Mean: 155.4	12 weeks	NR	Mean: 92.7	Mean %change:(-40.8) SE: 2.7	
	Arm 3: (M) SMV 20mg + Fenofibric acid 135mg	109	Mean: 157.9	12 weeks	NR	Mean: 116.6	Mean %change:(-24.0) SE: 1.9	NR
Shah, 2007[54]	Arm 1: (H) ATV 20mg daily	25	Mean: 101.7 SD: 34.8	3 months	25	Mean: 82.8 SD: 34.8	p<0.05	

	Arm 2: (H) SMV 40mg daily	23	Mean: 93.6 SD: 23.2	3 months	23	Mean: 77.0 SD: 27.1	p<0.05	
	Arm 3: (M) ATV 10mg + Fenofibrate 200 mg	21	Mean: 91.6 SD: 34.8	3 months	21	Mean: 87.0 SD: 19.3	NR	Arm1 vs Arm3 p<0.05
	Arm 4: (M) SMV 20mg + Fenofibrate 200mg	22	Mean: 92.4 SD: 23.2	3 months	22	Mean: 77.0 SD: 27.1	p<0.05	NR

Evidence Table E69. LDL goal attainment – fibrates

Author, Year	Group	Definition	Baseline N	Follow up timing	N at follow up	N (%) with event at follow up	Between group difference
Farnier, 2011 [52]	Arm 1: (M) SMV 20mg	Attainment of LDL<100mg/dL	144	12 weeks	NR	40 (28)	
	Arm 2: (L) PRV 40mg + Fenofibrate 160mg	Attainment of LDL<100mg/dL	145	12 weeks	NR	49 (34)	p=NS
Athyros, 2002 [51]	Arm1: (H) ATV 20mg	Attainment of LDL goal	131	12 months	131	(85)	
	Arm 2: (L) PRV 20mg + Gemfibrosil 1200mg	Attainment of LDL goal	133	12 months	133	(40)	
	Arm 3: (M) SMV 20mg + Gemfibrosil 1200mg	Attainment of LDL goal	129	12 months	129	(55)	
	Arm4: (M) SMV 20mg + Ciprofibrate 100mg	Attainment of LDL goal	129	12 months	129	(68)	
	Arm5: (L) PRV 20mg + Ciprofibrate 100mg	Attainment of LDL goal	132	12 months	132	(53)	

Evidence Table E70. HDL (mg/dL) outcome – fibrates

Author, Year	Group	Baseline N	Baseline outcome	Follow up timing	N at follow up	Outcome at follow up	Within group differences	Between group difference
Athyros, 2002 [51]	Arm1: (H) ATV 20mg	131	Mean: 36 SD: 2	12 months	131	NR	Mean % change: 6	
	Arm 2: (L) PRV 20mg + Gemfibrosil 1200mg	133	Mean: 36 SD: 2	12 months	133	NR	Mean % change: 15	NR
	Arm 3: (M) SMV 20mg + Gemfibrosil 1200mg	129	Mean: 36 SD: 2	12 months	129	NR	Mean % change: 20	NR
	Arm4: (M) SMV 20mg + Ciprofibrate 100mg	129	Mean: 37 SD: 2	12 months	129	NR	Mean % change: 14	NR
	Arm5: (L) PRV 20mg + Ciprofibrate 100mg	132	Mean: 35 SD: 1	12 months	132	NR	Mean % change: 17	NR
Farnier, 2011 [52]	Arm 1: (M) SMV 20mg	144	Mean: 45.0 SD: 10.1	12 weeks	144	Mean: 45.6 SD: 11.1	Mean % change=1.8 SE=1.3 P=0.013	
	Arm 2: (L) PRV 40mg + Fenofibrate 160mg	145	Mean: 45.8 SD: 10.0	12 weeks	145	Mean: 48.6 SD: 12.7	Mean% change=6.3 SE: 1.1 P<0.001	Difference= +4.5 p=0.008
Mohiuddin, 2009 [53]	Arm 1: (H) SMV 40mg	102	Mean: 38.5	12 weeks	102	Mean: 41.3	Mean % change=8.5 SE: 1.9	
	Arm 2: (H) SMV 80mg	52	Mean: 39.5	12 weeks	52	Mean: 41.5	Mean % change= 6.8 SE: 2.6	
	Arm 3: (M) SMV 20mg + Fenofibric acid 135mg	105	Mean: 37.2	12 weeks	105	Mean: 43.9	Mean % change=17.8 SE: 1.9	NR
Shah, 2007[54]	Arm 1: (H) ATV 20mg daily	25	Mean: 34.8 SD: 9.3	3 months	25	Mean: 41.8 SD: 7.7	p<0.05	
	Arm 2: (H) SMV 40mg daily	23	Mean: 34.8 SD: 8.5	3 months	23	Mean: 43.7 SD: 11.6	p<0.05	Arm1 vs Arm2 p<0.05
	Arm 3: (M) ATV 10mg +	21	Mean: 34.8 SD: 9.3	3 months	21	Mean: 47.2 SD: 7.7	p<0.05	Arm1 vs Arm3 p<0.05

Author, Year	Group	Baseline N	Baseline outcome	Follow up timing	N at follow up	Outcome at follow up	Within group differences	Between group difference
	Fenofibrate 200 mg							
	Arm 4: (M) SMV 20mg + Fenofibrate 200mg	22	Mean: 34.8 SD: 8.5	3 months	22	Mean: 43.7 SD: 11.6	p<0.05	Arm1 vs Arm3 p<0.05

Evidence Table E71. Total cholesterol:HDL ratio – fibrates

Author, Year	Group	Baseline N	Baseline outcome	Follow up timing	N at follow up	Outcome at follow up	Within group differences	Between group difference
Athyros, 2002 [51]	Arm1: (H) ATV 20mg	131	Mean: 8.4 SD:0.8	12 months	131	NR	Mean % change: (-44)	
	Arm 2: (L) PRV 20mg + Gemfibrosil 1200mg	133	Mean:8.7 SD: 0.8	12 months	133	NR	Mean % change: (-40)	NR
	Arm 3: (M) SMV 20mg + Gemfibrosil 1200mg	129	Mean:8.3 SD: 0.8	12 months	129	NR	Mean % change: (-46)	Arm1 vs Arm 3 p<0.01
	Arm4: (M) SMV 20mg + Ciprofibrate 100mg	129	Mean: 8.2 SD:0.7	12 months	129	NR	Mean % change: (-46)	Arm1 vs Arm 4 p<0.01
	Arm5: (L) PRV 20mg + Ciprofibrate 100mg	132	Mean:8.5 SD:0.7	12 months	132	NR	Mean % change: (-44)	NR
Shah, 2007[54]	Arm 1: (H) ATV 20mg daily	25	Mean: 4.33 SD: 1.3	3 months	25	Mean: 3.71 SD: 1.2	p<0.05	
	Arm 2: (H) SMV 40mg daily	23	Mean: 4.42 SD: 1.3	3 months	23	Mean: 3.66 SD: 1.8	NR	
	Arm 3: (M) ATV 10mg + Fenofibrate 200 mg	21	Mean: 4.41 SD: 1.4	3 months	21	Mean: 3.42 SD: 0.7	p<0.05	NR
	Arm 4: (M) SMV 20mg + Fenofibrate 200mg	22	Mean: 4.37 SD: 1.3	3 months	22	Mean: 3.66 SD: 1.8	p<0.05	NR

Evidence Table E72. Triglycerides and non-HDL-c among diabetes subgroup – fibrates

Author, Year	Group	Baseline N	Baseline outcome	Follow up timing	N at follow up	Outcome at follow up	Within group differences	Between group difference
Farnier, 2011 [52]	Arm 1: (M) SMV 20mg	144	Mean non-HDL: 168.4 SD: 32.5	12 weeks	144	Mean non-HDL: 154.5 SD: 36.3	Mean % change: (-6.8) SE: 1.8 p<0.001	
	Arm 2: (L) PRV 40mg + Fenofibrate 160mg	145	Mean non-HDL: 165.9 SD: 29.3	12 weeks	145	Mean non-HDL: 143.3 SD: 42.8	Mean % change: (-12.9) SE: 1.8 p<0.001	Difference mean % change: (-6.1) p=0.008
Farnier, 2011 [52]	Arm 1: (M) SMV 20mg	144	Mean TG: 277.7 SD: 117.5	12 weeks	144	Mean TG: 281.8 SD: 156.8	Mean % change: 5.0 SE: 3.6 p=0.25	
	Arm 2: (L) PRV 40mg + Fenofibrate 160mg	145	Mean TG: 261.4 SD: 93.1	12 weeks	145	Mean TG: 182.9 SD: 124.2	Mean % change: -28.6 SE: 3.7 p<0.001	Difference mean % change: (-33.5) p<0.001

Evidence Table E73. Treatment adherence – fibrates

Author, Year	Group	Definition	Baseline N	Follow up timing	N at follow up	N (%) with event at follow up	Between group difference
Farnier, 2011 [52]	Arm 1: (M) SMV 20mg	>80% compliance	NR	12 weeks	NR	(98)	
	Arm 2: (L) PRV 40mg + Fenofibrate 160mg	>80% compliance	NR	12 weeks	NR	(99)	NR

Evidence Table E74. Occurrence of at least one adverse event – fibrates

Author, Year	Group	Baseline N	Follow up timing	N at follow up	N (%) with event at follow up	Between group difference
Farnier, 2011 [52]	Arm 1: (M) SMV 20mg	NR	12 weeks	146	22 (15)	
	Arm 2: (L) PRV 40mg + Fenofibrate 160mg	NR	12 weeks	145	25 (17)	p=NS

Evidence Table E75. Elevated liver transaminases – fibrates

Author, Year	Group	Definition	Baseline N	Follow up timing	N at follow up	N (%) with event at follow up	Between group difference
Athyros, 2002 [51]	Arm1: (H) ATV 20mg	AST and/or ALT>3 times ULN	131	12 months	NR	0	
	Arm 2: (L) PRV 20mg + Gemfibrosil 1200mg	AST and/or ALT>3 times ULN	133	12 months	NR	1 (0.8)	NR
	Arm 3: (M) SMV 20mg + Gemfibrosil 1200mg	AST and/or ALT>3 times ULN	129	12 months	NR	3 (2.3)	NR
	Arm4: (M) SMV 20mg + Ciprofibrate 100mg	AST and/or ALT>3 times ULN	129	12 months	NR	3 (2.3)	NR
	Arm5: (L) PRV 20mg + Ciprofibrate 100mg	AST and/or ALT>3 times ULN	132	12 months	NR	0	NR
Mohiuddin, 2009 [53]	Arm 1: (H) SMV 40mg	AST and/or ALT>3 times ULN	NR	12 weeks	116	0	
	Arm 2: (H) SMV 80mg	AST and/or ALT>3 times ULN AST/ALT>	NR	12 weeks	59	1 (1.7)	
	Arm 3: (M) SMV 20mg + Fenofibric acid 135mg	AST and/or ALT>3 times ULN AST/ALT>	NR	12 weeks	119	0	NR

Evidence Table E76. Elevated creatinine phosphokinase (CPK) – fibrates

Author, Year	Group	Definition	Baseline N	Follow up timing	N at follow up	N (%) with event at follow up	Between group difference
Athyros, 2002 [51]	Arm1: (H) ATV 20mg		131	12 months	NR	0	
	Arm 2: (L) PRV 20mg + Gemfibrosil 1200mg		133	12 months	NR	1 (0.8)	NR
	Arm 3: (M) SMV 20mg + Gemfibrosil 1200mg		129	12 months	NR	1 (0.8)	NR
	Arm4: (M) SMV 20mg + Ciprofibrate 100mg		129	12 months	NR	0	NR
	Arm5: (L) PRV 20mg + Ciprofibrate 100mg		132	12 months	NR	0	NR
Farnier, 2011 [52]	Arm 1: (M) SMV 20mg	CPK> 5 times ULN	NR	12 weeks	146	0	
	Arm 2: (L) PRV 40mg + Fenofibrate 160mg	CPK> 5 times ULN	NR	12 weeks	145	0	NR
Mohiuddin, 2009 [53]	Arm 1: (H) SMV 40mg	CPK>10 times ULN	NR	12 weeks	116	2 (1.7)	
	Arm 2: (H) SMV 80mg	CPK>10 times ULN CPK>	NR	12 weeks	59	0	
	Arm 3: (M) SMV 20mg + Fenofibric acid 135mg	CPK>10 times ULN CPK>	NR	12 weeks	119	0	NR

Evidence Table E77. Rhabdomyolysis – fibrates

Author, Year	Group	Definition	Baseline N	Follow up timing	N at follow up	N (%) with event at follow up	Between group difference
Mohiuddin, 2009 [53]	Arm 1: (H) SMV 40mg	NR	NR	12 weeks	116	0	
	Arm 2: (H) SMV 80mg	NR	NR	12 weeks	59	0	
	Arm 3: (M) SMV 20mg + Fenofibric acid 135mg	NR	NR	12 weeks	119	0	NR

Evidence Table E78. Myalgia – fibrates

Author, Year	Group	Definition	Baseline N	Follow up timing	N at follow up	N (%) with event at follow up	Between group difference
Mohiuddin, 2009 [53]	Arm 1: (H) SMV 40mg		NR	12 weeks	116	6 (5)	
	Arm 2: (H) SMV 80mg		NR	12 weeks	59	3 (5)	
	Arm 3: (M) SMV 20mg + Fenofibric acid 135mg		NR	12 weeks	119	5 (4)	NR
Shah, 2007[54]	Arm 1: (H) ATV 20mg daily	Occurrence of muscle pain	25	3 months	25	0	
	Arm 2: (H) SMV 40mg daily	Occurrence of muscle pain	23	3 months	23	2	
	Arm 3: (M) ATV 10mg + Fenofibrate 200 mg	Occurrence of muscle pain	21	3 months	21	0	NR
	Arm 4: (M) SMV 20mg + Fenofibrate 200mg	Occurrence of muscle pain	22	3 months	22	0	NR

Evidence Table E79. Acute kidney injury (AKI) – fibrates

Author, Year	Group	Definition	Baseline N	Follow up timing	N at follow up	N (%) with event at follow up	Between group difference
Farnier, 2011 [52]	Arm 1: (M) SMV 20mg	Cr>20 mg/mL or CrCl< 50 ml/min	NR	12 weeks	146	0	
	Arm 2: (L) PRV 40mg + Fenofibrate 160mg	Cr>20 mg/mL or CrCl< 50 ml/min	NR	12 weeks	145	0	NR
Mohiuddin, 2009 [53]	Arm 1: (H) SMV 40mg	Cr >50% increase and increased above ULN	NR	12 weeks	116	0	
	Arm 2: (H) SMV 80mg	Cr >50% increase and increased above ULN	NR	12 weeks	59	0	
	Arm 3: (M) SMV 20mg + Fenofibric acid 135mg	Cr >50% increase and increased above ULN	NR	12 weeks	119	4 (3.4)	NR

Evidence Table E80. Study quality assessment – fibrates

Author, Year	2009 CER Jadad Score	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14
Athyros, 2002 [51]	1	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Farnier, 2011 [52]	NA	L	L	L	L	L	L	L	N	Y	Y	Y	Y	Y	N
Mohuiddin, 2009 [53]	NA	U	U	L	L	L	L	L	N	Y	Y	Y	U	Y	N
Shah, 2007[54]	NA	U	H	H	H	L	U	L	N	Y	U	U	U	Y	N

CER comparative effectiveness report; H high; L low; NA not applicable; N no; U unclear or unsure.

Q1. What is the risk of selection bias (biased allocation to interventions) due to inadequate generation of a randomized sequence?
Q2. What is the risk of selection bias (biased allocation to interventions) due to inadequate concealment of allocations before assignment?
Q3. For each main outcome or class of outcomes, what is the risk of performance bias due to knowledge of the allocated interventions by participants and personnel during the study (lack of study participant and personnel blinding)?
Q4. Was the care provider blinded to the intervention?
Q5. For each main outcome or class of outcomes, what is the risk of detection bias due to knowledge of the allocated interventions by outcome assessment (lack of outcome assessor blinding)?
Q6. For each main outcome or class of outcomes, what is the risk of attrition bias due to amount, nature, or handling of incomplete outcome data?
Q7. What is the risk of reporting bias due to selective outcome reporting?
Q8. Are there other biases due to problems not covered in 1-6?
Q9. Were all randomized participants analyzed in the group to which they were allocated?
Q10. Were the groups similar at baseline regarding the most important prognostic indicators?
Q11. Were co-interventions avoided or similar?
Q12. Was the compliance acceptable in all groups?
Q13. Was the timing of the outcome assessment similar in all groups?
Q14. Are there other risks of bias?

Evidence Table E81. Study characteristics – niacin

Author, Year **Trial #, "Acronym"**	**Study Design** **Site(s)**	**Inclusion Criteria**	**Participant Use of Lipid-Modifying Agents Prior to Trial**	**Treatment Duration** **Washout Period** **Run-In Period**	**Arms (Potency)**	**Subgroup Analyses**	**Pharmaceutical Industry Support** **Conflict of interest disclosure by author**
Airan-Javia, 2009[55] NCT00307307	Parallel Arm RCT Multicenter North America	-Patients with carotid atherosclerosis (>30% stenosis on US) -Age 18-90 years -LDL-c>100mg/dL or LDL-c>80mg/dL if HDL-c<49mg/dL -BP<170/90 -Negative pregnancy test (females) -No history of CVA, TIA, MI, UA, or critical limb ischemia in the last 3 months -No poorly controlled DM (HbA1c>8%) -No contraindications to MRI -No history of adverse events on statins or niacin -No history of myositis or abnormal LFTs -No active infection or malignancy -No need for combination lipid-lowering therapy	-Current statin discontinued at randomization -Baseline laboratory lipid measurements reflect prior statin use	12 months NR None	Arm1: (M)* SMV 20mg Arm 2: (H) SMV 80mg Arm 3: (M) N-ER 2g +SMV 20mg [N-ER dose titrated from 500mg to 2g, as tolerated over initial 3 months]	None	Study funded in part by pharmaceutical companies. Authors have no pharmaceutical company COI disclosures.
Bays, 2003[56] "ADVOCATE"	Parallel Arm RCT Multicenter North America	-Patients with dyslipidemia defined as 2 consecutive baseline LDL>=160 mg/dl without CAD or >=130 mg/dl with CAD; TG<300mg/dL and HDL<45 mg/dL in men and <50mg/dL in women -Age 18-70 years -Women must be using an effective means of contraception -No uncontrolled hypertension; NYHA class III/IV CHF; type 1 or 2 DM; UA, MI, CBG, percutaneous transluminal coronary angioplasty, or CVA within prior 6 months	-Lipid modifying drugs discontinued 6 weeks before randomization. -Baseline laboratory lipid measurements reflect dietary run in	16 weeks NR 4 week dietary run in	Arm 1: (H) ATV 40mg Arm 2: (H) SMV 40mg Arm 3: (M) N-ER 1g +LOV 40mg Arm 4: (M) N-ER 2g +LOV 40mg	None	Study funded by pharmaceutical companies. Authors have pharmaceutical company COI disclosures.

Author, Year Trial #, "Acronym"	Study Design Site(s)	Inclusion Criteria	Participant Use of Lipid-Modifying Agents Prior to Trial	Treatment Duration Washout Period Run-In Period	Arms (Potency)	Subgroup Analyses	Pharmaceutical Industry Support Conflict of interest disclosure by author
		-No history of substance abuse or dependence within 12 months of screening, consumption of >14 alcoholic drinks per week, uncontrolled psychiatric disease. -No active gallbladder disease; hepatic dysfunction; renal insufficiency; fasting glucose >=115mg/dL; active gout symptoms or uric acid >1.3x ULN; active peptic ulcer disease; fibromyalgia; cancer within the previous 5 years (except for basal cell carcinoma). -No known prior allergy or intolerability to any of the study drugs; participation in another investigational study within 30 days of screening, probucol administration within the previous year, or any condition or laboratory abnormality which might be adversely affected by the study procedures or medications.			[Doses of statin and N-ER titrated up during study period to final doses in all arms by week 12]		
Gardner, 1996[57] NR	Parallel Arm RCT Single Center North America	-Patients with diagnosis of hyperlipidemia -Age 18-75 years -LDL >=130 mg/dl or >=100mg/dL in CAD patients despite diet and statin run in periods -TG<=350mg/dL -Patients must discontinue their previous lipid-lowering drug therapy -AST and ALT < 2x ULN -Women of childbearing potential had to practice birth control with oral contraceptives, intrauterine devices,	-Lipid modifying drugs discontinued 4 weeks prior to baseline assessment. -Baseline laboratory lipid measurements reflect dietary and medication run in	6 weeks NR 4 week dietary run in followed by 4 weeks of LOV 20mg run in	Arm 1: (M) LOV 40mg Arm 2: (L) N 1.5g +LOV 20mg [N was titrated up over a period of 2 weeks to final dose]	None	Study funded by pharmaceutical companies. Authors report no pharmaceutical company COI disclosures.

Author, Year Trial #, "Acronym"	Study Design Site(s)	Inclusion Criteria	Participant Use of Lipid-Modifying Agents Prior to Trial	Treatment Duration Washout Period Run-In Period	Arms (Potency)	Subgroup Analyses	Pharmaceutical Industry Support Conflict of interest disclosure by author
		abstinence, diaphragms, or mechanical barriers. -No history of acute or chronic hepatitis and/or cardiovascular complications including MI within the last 12 months, UA, CHF, and cardiovascular surgery or coronary angioplasty within the last 6 months. -No secondary hyperlipidemias due to alcoholism, autoimmune disease, dysglobinemia, glycogen storage disease, hypothyroidism, type 1 diabetes mellitus, macroglobulinemia, multiple myeloma, nephrotic syndrome, obstructive liver disease, or chronic pancreatitis -Not taking steroid hormones (except estrogen-progesterone therapy), thyroid hormones (except for replacement therapy), erythromycin, or cyclosporine					
Hunninghake, 2003[58] NR	Parallel Arm RCT Multicenter North America	-Patients with type IIA hyperlipidemia or type IIB hyperlipidemia with elevated LDL-C levels based on ATP II guidelines: -≥130 mg/dl CAD or type 2 DM patients -≥160 mg/dl no CAD or DM, but 2+ CAD risk factors -≥190 mg/dl <2 CAD risk factors -Age≥ 18 years -TG < 800 mg/dl -No severe hypertension, a recent major cardiovascular or cerebrovascular event, type 1 or	-Lipid modifying drugs discontinued 4 weeks before randomization. -Baseline laboratory lipid measurements reflect dietary run in	28 weeks NR 4 week dietary run in	Arm 1: (M) LOV 40mg Arm 2: (L) N-ER 1g +LOV 20mg Arm 3: (M)* N-ER 2g +LOV 40mg Arm 4: (NA)* N-ER 2g	None	Study funded by pharmaceutical companies. Authors have pharmaceutical company COI disclosures.

Author, Year Trial #, "Acronym"	Study Design Site(s)	Inclusion Criteria	Participant Use of Lipid-Modifying Agents Prior to Trial	Treatment Duration Washout Period Run-In Period	Arms (Potency)	Subgroup Analyses	Pharmaceutical Industry Support Conflict of interest disclosure by author
		uncontrolled type 2 diabetes mellitus -No hepatic dysfunction, renal disease, biliary disease, active peptic ulcer disease, gout, or cancer -No inability to withdraw concomitant lipid-altering drug therapy, probucol treatment within the last year, concurrent use of medications with hepatic or myopathic side effects -No women of childbearing potential not using contraception			[Doses of LOV and N-ER titrated up during study period to final doses in all arms by week 21]		
Insull, 2004[59] NR	Parallel Arm RCT Multicenter North America	-Patients with type IIa or IIb primary hyperlipidemia -Age 21 years or older -LDL-C>=130mg/dL in patients with CHD or diabetes; >=160mg/dL in patients with 2+ CHD risk factors; >=190 mg/dL in patients with less than 2 risk factors -TG < 800 mg/dL -No recent (within 6 months) MI, UA, CVA, or revascularization; CHF, arterial bleeding, severe hypertension -No hepatic dysfunction; renal disease; active peptic ulcer, or gallbladder disease; type 1 or uncontrolled type 2 diabetes mellitus; active gout; substance abuse -No breast-feeding women or women of childbearing potential using inadequate contraception -No concomitant use of agents with adverse effects on hepatic function, skeletal muscle, or creatine kinase; agents metabolized by the	-Lipid modifying drugs discontinued 6 weeks before randomization. -Baseline laboratory lipid measurements reflect dietary run in	20 weeks NR 4 week dietary run in	Arm 1: (M) LOV 40mg Arm 2: (L) N-ER 2.5g +LOV 10mg Arm 3: (L) N-ER 2.5g +LOV 20mg Arm 4: (M)* N-ER 2.5g +LOV 40mg Arm 5: (NA)* N-ER 2.5g [Doses of LOV and N-ER titrated up during study period to final doses in all	None	Study funded by pharmaceutical companies. Authors have pharmaceutical company COI disclosures.

Author, Year Trial #, "Acronym"	Study Design Site(s)	Inclusion Criteria	Participant Use of Lipid-Modifying Agents Prior to Trial	Treatment Duration Washout Period Run-In Period	Arms (Potency)	Subgroup Analyses	Pharmaceutical Industry Support Conflict of interest disclosure by author
		cytochrome P-450			arms by week 16]		

ALT alanine amiotransferase; AST aspartate aminotransferase; BP blood pressure; CABG coronary artery bypass graft; COI conflicts of interest; CHD coronary heart disease; CPK creatine phosphokinase; CVA cerebrovascular accident; DM diabetes mellitus; DVT deep venous thrombosis; HbA1c hemoglobin A1c; HDL high density lipoprotein; LDL low density lipoprotein; LFTs liver function tests; MI myocardial infarction; MRI magnetic resonance imaging; NCEP ATP III National Cholesterol Education Program Adult Treatment Panel III; N-ER Niacin Extended Release; NR not reported; NYHA class III or IV CHF New York Heart Association class III or IV congestive heart failure; PAD peripheral arterial disease; PUD peptic ulcer disease; RCT randomized controlled trial; SMV simvastatin; TIA transient ischemic attack; UA unstable angina; ULN upper limit of normal; US ultrasound

*This arm included only in population characteristics to fully describe study population; however, will not be included in further description or analyses as it is ineligible.

Evidence Table E82. Baseline population characteristics – niacin

Author, Year	Arms (Potency)	N	Age	Female N (%)	Race N (%)	Smoking Status N (%)	Prior CHD N (%)	Prior CVA N (%)	Prior REVASC N (%)	DM N (%)	LDL	Between Group Differences
Airan-Javia, 2009[55]	Arm1: (M)* SMV 20mg Arm 2: (H) SMV 80mg Arm 3: (M) N-ER 2g +SMV 20mg	Arm 1: 25 Arm 2: 24 Arm 3: 26	Arm 1: Median; 71 IQR; 66-76 Arm 2: Median; 72.5 IQR; 65-76.5 Arm 3: Mean; 70.5 IQR; 60-80	Arm 1: 8 (32%) Arm 2: 5 (21%) Arm 3: 8 (31%)	Arm 1: White; 21 (84%) Black; 4 (16%) Hispanic: 0 Arm 2: White; 23 (96%) Black; 1 (4%) Hispanic: 0 Arm 3: White; 16 (61%) Black; 9 (35%) Hispanic; 1 (4%)	NR	NR	NR	NR	Arm 1: 3 (12%) Arm 2: 3 (13%) Arm 3: 8 (31%)	Arm 1: Median; 102 mg/dL IQR; 97-120 Arm 2: Median; 107 mg/dL IQR; 89-133 Arm 3: Median; 124 mg/dL IQR; 104-143	Significant between group differences by race ($p<0.05$).
Bays, 2003[56]	Arm 1: (H) ATV 40mg Arm 2: (H) SMV 40mg Arm 3: (M) N-ER 1g +LOV 40mg Arm 4: (M) N-ER 2g +LOV 40mg	Arm 1: 82 Arm 2: 76 Arm 3: 79 Arm 4: 78	Arm 1: Mean; 52 SE; 1.0 Arm 2: Mean; 54 SE; 1.2 Arm 3: Mean; 53 SE; 1.2 Arm 4: Mean; 52 SE; 1.2	Arm 1: 23 (28%) Arm 2: 19 (25%) Arm 3: 22 (28%) Arm 4: 24 (31%)	Arm 1: White; 71 (87%) Arm 2: White; 64 (84%) Arm 3: White; 70 (89%) Arm 4: White; 69 (88%)	NR	Arm 1: 16 (20%) Arm 2: 18 (24%) Arm 3: 17 (22%) Arm 4: 15 (19%)	NR	NR	NR	Arm 1: Mean; 196 mg/dL SE; 3.9 Arm 2: Mean; 192 mg/dL SE; 4.5 Arm 3: Mean; 190 mg/dL SE; 3.6 Arm 4: Mean; 189 mg/dL SE; 3.0	No significant between group differences

Author, Year	Arms (Potency)	N	Age	Female N (%)	Race N (%)	Smoking Status N (%)	Prior CHD N (%)	Prior CVA N (%)	Prior REVASC N (%)	DM N (%)	LDL	Between Group Differences
Gardner, 1996[57]	Arm 1: (M) LOV 40mg Arm 2: (L) N 1.5g +LOV 20mg	Arm 1: 14 Arm 2: 14	Arm 1: Mean; 53 SD; 9.8 Arm 2: Mean; 49 SD; 10.4	Arm 1: 11 (79%) Arm 2: 5 (36%)	NR	NR	NR	NR	NR	NR	Arm 1: Mean; 159 mg/dL SD; 48 Arm 2; Mean; 148 mg/dL SD; 19	No significant between group differences.
Hunninghake, 2003[58]	Arm 1: (M) LOV 40mg Arm 2: (L) N-ER 1g +LOV 20mg Arm 3: (M)* N-ER 2g +LOV 40mg Arm 4: (NA)* N-ER 2g	Arm 1: 61 Arm 2: 57 Arm 3: 57 Arm 4: 61	Arm 1: Mean; 61 SE; 1.3 Arm 2: Mean; 59 SE; 1.6 Arm 3: Mean; 60 SE; 1.6 Arm 4: Mean; 58 SE; 1.4	Arm 1: 22 (36%) Arm 2: 26 (46%) Arm 3: 25 (44%) Arm 4: 33 (54%)	Arm 1: White; 51 (84%) Black; 3 (5%) Hispanic; 4 (7%) Asian; 3 (5%) Arm 2: White; 50 (88%) Black; 2 (4%) Hispanic; 5 (9%) Asian; 0 Arm 3: White; 49 (86%) Black; 4 (7%) Hispanic; 3 (5%) Asian; 1 (2%) Arm 4: White; 55 (90%) Black; 3 (5%) Hispanic; 2 (3%) Asian; 1 (2%)	NR	Arm 1: 40 (65%) Arm 2: 39 (69%) Arm 3: 40 (70%) Arm 4: 44 (73%) [Patients with 2 or more CHD risk factors]	NR	NR	NR	Arm 1: Mean; 186 mg/dL SE; 4.7 Arm 2: Mean; 192 mg/dL SE; 6.0 Arm 3: Mean; 191 mg/dL SE; 4.5 Arm 4: Mean; 190 mg/dL SE; 4.1	No significant between group differences.

Author, Year	Arms (Potency)	N	Age	Female N (%)	Race N (%)	Smoking Status N (%)	Prior CHD N (%)	Prior CVA N (%)	Prior REVASC N (%)	DM N (%)	LDL	Between Group Differences
Insull, 2004[59]	Arm 1: (M) LOV 40mg Arm 2: (L) N-ER 2.5g +LOV 10mg Arm 3: (L) N-ER 2.5g +LOV 20mg Arm 4: (M)* N-ER 2.5g +LOV 40mg Arm 5: (NA)* N-ER 2.5g	Arm 1: 33 Arm 2: 34 Arm 3: 34 Arm 4: 32 Arm 5: 31	Arm 1: Mean; 58 SE; 2.4 Arm 2: Mean; 59 SE; 1.9 Arm 3: Mean; 61 SE; 1.8 Arm 4: Mean; 60 Se; 2.0 Arm 5: Mean; 58 SE; 2.0	Arm 1: 15 (45%) Arm 2: 17 (50%) Arm 3: 16 (47%) Arm 4: 17 (53%) Arm 5: 14 (45%)	Arm 1: White; 29 (88%) Black; 3 (9%) Hispanic; 0 Other; 1 (3%) Arm 2: White; 29 (85%) Black; 5 (15%) Hispanic; 0 Other; 0 Arm 3: White; 26 (74%) Black; 7 (21%) Hispanic; 0 Other; 2 (6%) Arm 4: White; 27 (84%) Black; 4 (13%) Hispanic; 0 Other; 1 (3%) Arm 5: White; 25 (80%) Black; 3 (10%) Hispanic; 1 (3%) Other; 2 (6%)	NR	Arm 1: 22 (66 %) Arm 2: 25 (74%) Arm 3: 24 (70%) Arm 4: 24 (76%) Arm 5: 23 (73%) [Patients with 2 or more CHD risk factors]	NR	NR	NR	Arm 1: Mean; 196 mg/dL SE; 4.6 Arm 2: Mean; 200 mg/dL Se; 7.1 Arm 3: Mean; 191 mg/dL SE; 5.4 Arm 4: Mean; 205 mg/dL SE; 7.7 Arm 5: Mean; 202 mg/dL SE; 6.8	NR

CHD coronary heart disease; CVA cerebrovascular accident; DM diabetes mellitus; IQR interquartile range; LDL low density lipoprotein; LOV Lovastatin; N-ER Niacin Extended Release; NR not reported; REVASC revascularization procedure; RSV Rosuvastatin; SMV Simvastatin.
*This arm included only in population characteristics to fully describe study population; however, will not be included in further description or analyses as it is ineligible.

Evidence Table E83. All cause mortality – niacin

Author, Year	Arm (Potency)	Outcome Units	Timepoint(s)	N at Timepoint(s)	Outcome at Timepoint(s)	Between Arm Comparisons
Hunninghake, 2003[58]	Arm 1: (M) LOV 40mg	Count Deaths	28 weeks	NR	n: 1	
	Arm 2: (L) N-ER 1g +LOV 20mg	Count Deaths	28 weeks	NR	n: 1	NR

LOV Lovastatin; N-ER Niacin Extended Release; NR not reported; SMV Simvastatin.

Evidence Table E84. Vascular deaths – niacin

Author, Year	Arm (Potency)	Outcome Units	Timepoint(s)	N at Timepoint(s)	Outcome at Timepoint(s)	Between Arm Comparisons
Hunninghake, 2003[58]	Arm 1: (M) LOV 40mg	Count Vascular Deaths	28 weeks	NR	n: 1	
	Arm 2: (L) N-ER 1g +LOV 20mg	Count Vascular Deaths	28 weeks	NR	n: 1	NR

LOV Lovastatin; N-ER Niacin Extended Release; NR not reported; SMV Simvastatin.

Evidence Table E85. Acute coronary syndrome – niacin

Author, Year	Arm (Potency)	Outcome Units	Timepoint(s)	N at Timepoint(s)	Outcome at Timepoint(s)	Between Arm Comparisons
Airan-Javia, 2009[55]	Arm 2: (H) SMV 80mg	Count Occurrence of ACS	12 months	24	# ACS events: 1	
	Arm 3: (M) N-ER 2g +SMV 20mg	Count Occurrence of ACS	12 months	26	# ACS events: 0	NR

ACS acute coronary syndrome;IQR interquartile range; N-ER Niacin Extended Release; NR not reported; SMV Simvastatin.

Evidence Table E86. LDL outcome – niacin

Author, Year	Arm (Potency)	Outcome Units	Baseline N	Baseline Outcome	Timepoint(s)	N at Timepoint(s)	Outcome at Timepoint(s)	Within Arm Comparisons	Between Arm Comparisons
Airan-Javia, 2009[55]	Arm 2: (H) SMV 80mg	Continuous LDL – measured mg/dL	24	Median: 107 mg/dL IQR: 89-133 mg/dL	6 months 12 months	NR NR	Median: 89 mg/dL Median: 81 mg/dL	% Change from baseline: -17% % Change from baseline: -24%	
	Arm 3: (M) N-ER 2g +SMV 20mg	Continuous LDL – measured mg/dL	26	Median: 124 mg/dL IQR:104-143 mg/dL	6 months 12 months	NR NR	Median: 77 mg/dL Median: 75 mg/dL	% Change from baseline: -37% % Change from baseline: -39%	p-value=0.24 comparing Arm 2 vs Arm 3 at 12 months
Bays, 2003[56]	Arm 1: (H) ATV 20mg	Continuous LDL – calculated mg/dL	82	Mean: 196 mg/dL SE: 3.9	12 weeks	NR	NR	% Change from baseline: -45%	
	Arm 3: (M) N-ER 1g +LOV 40mg	Continuous LDL – calculated mg/dL	79	Mean: 190 mg/dL SE: 3.6	12 weeks	NR	NR	% Change from baseline: -42%	NR
	Arm 4: (M) N-ER 1.5g +LOV 40mg	Continuous LDL – calculated mg/dL	78	Mean: 189 mg/dL SE: 3.0	12 weeks	NR	NR	% Change from baseline: -42%	NR
Bays, 2003[56]	Arm 1: (H) ATV 40mg	Continuous LDL – calculated	82	Mean: 196 mg/dL SE: 3.9	16 weeks	NR	NR	% Change from baseline: -49%	

Author, Year	Arm (Potency)	Outcome Units	Baseline N	Baseline Outcome	Timepoint(s)	N at Timepoint(s)	Outcome at Timepoint(s)	Within Arm Comparisons	Between Arm Comparisons
		mg/dL							
	Arm 2: (H) SMV 40mg	Continuous LDL – calculated mg/dL	76	Mean: 192 mg/dL SE: 4.5	16 weeks	NR	NR	% Change from baseline: -39%	P<0.05 comparing arms 1 and 2
	Arm 3: (M) N-ER 1g +LOV 40mg	Continuous LDL – calculated mg/dL	79	Mean: 190 mg/dL SE: 3.6	16 weeks	NR	NR	% Change from baseline: -39%	P<0.05 comparing arms 1 and 3
	Arm 4: (M) N-ER 2g +LOV 40mg	Continuous LDL – calculated mg/dL	78	Mean: 189 mg/dL SE: 3.0	16 weeks	NR	NR	% Change from baseline: -42%	P<0.001 comparing arms 1 and 4
Gardner, 1996[57]	Arm 1: (M) LOV 40mg	Continuous LDL – NR mg/dL	14	Mean: 159 mg/dL SD: 48	6 weeks	14	Mean: 146 mg/dL SD: 46	% Change from baseline: -8%	
	Arm 2: (L) N 1.5g +LOV 20mg	Continuous LDL – NR mg/dL	14	Mean: 148 mg/dL SD: 19	6 weeks	14	Mean: 135 mg/dL SD: 22	% Change from baseline: -8%	P>0.05 comparing Arm 1 and Arm 2 at 6 weeks.
Hunninghake, 2003[58]	Arm 1: (M) LOV 40mg	Continuous LDL – calculated	61	Mean: 186 mg/dL SE: 4.7	28 weeks	NR	NR	% Change from baseline: -32%	

Author, Year	Arm (Potency)	Outcome Units	Baseline N	Baseline Outcome	Timepoint(s)	N at Timepoint(s)	Outcome at Timepoint(s)	Within Arm Comparisons	Between Arm Comparisons
		mg/dL							
	Arm 2: (L) N-ER 1g +LOV 20mg	Continuous LDL – calculated mg/dL	57	Mean: 192 mg/dL SE: 6.0	28 weeks	NR	NR	% Change from baseline: -28%	NR
Insull, 2004[59]	Arm 1: (M) LOV 40mg	Continuous LDL – calculated mg/dL	33	Mean: 196 mg/dL SE: 4.6	20 weeks	NR	NR	% Change from baseline: -24% SE: 2.4	
	Arm 2: (L) N-ER 2.5g +LOV 10mg	Continuous LDL – calculated mg/dL	34	Mean: 200 mg/dL SE: 7.1	20 weeks	NR	NR	% Change from baseline: -36% SE: 2.4	NR
	Arm 3: (L) N-ER 2.5g +LOV 20mg	Continuous LDL – calculated mg/dL	34	Mean: 191 mg/dL SE: 5.4	20 weeks	NR	NR	% Change from baseline: -36% SE: 4.4	NR

ATV Atorvastatin; IQR interquartile range; LDL low density lipoprotein; LOV Lovastatin; N-ER Niacin Extended Release; NR not reported; RSV Rosuvastatin; SMV Simvastatin.

Evidence Table E87. HDL outcome – niacin

Author, Year	Arm (Potency)	Outcome Units	Baseline N	Baseline Outcome	Timepoint(s)	N at Timepoint(s)	Outcome at Timepoint(s)	Within Arm Comparisons	Between Arm Comparisons
Airan-Javia, 2009[55]	Arm 2: (H) SMV 80mg	Continuous HDL – measured mg/dL	24	Median: 41 mg/dL IQR: 34-49 mg/dL	6 months 12 months	NR NR	Median: 42 mg/dL Median: 41 mg/dL	% Change from baseline: +2% % Change from baseline: 0%	
	Arm 3: (M) N-ER 2g +SMV 20mg	Continuous HDL – measured mg/dL	26	Median: 47 mg/dL IQR: 35-57mg/dL	6 months 12 months	NR NR	Median: 55 mg/dL Median: 56 mg/dL	% Change from baseline: +17% % Change from baseline: +18%	p-value=0.001 comparing Arm 2 vs Arm 3 at 12 months
Bays, 2003[56]	Arm 1: (H) ATV 20mg	Continuous HDL – measured mg/dL	82	Mean: 38 mg/dL SE: 0.6	12 weeks	NR	NR	% Change from baseline: +4%	
	Arm 3: (M) N-ER 1g +LOV 40mg	Continuous HDL – measured mg/dL	79	Mean: 38 mg/dL SE: 0.6	12 weeks	NR	NR	% Change from baseline: +19%	P<0.05 comparing arms 1 and 3
	Arm 4: (M) N-ER 1.5g +LOV 40mg	Continuous HDL – measured mg/dL	78	Mean: 39 mg/dL SE: 0.6	12 weeks	NR	NR	% Change from baseline: +24%	P<0.05 comparing arms 1 and 4
Bays, 2003[56]	Arm 1: (H) ATV 40mg	Continuous HDL – measured	82	Mean: 38 mg/dL SE: 0.6	16 weeks	NR	NR	% Change from baseline: +6%	

Author, Year	Arm (Potency)	Outcome Units	Baseline N	Baseline Outcome	Timepoint(s)	N at Timepoint(s)	Outcome at Timepoint(s)	Within Arm Comparisons	Between Arm Comparisons
		mg/dL							
	Arm 2: (H) SMV 40mg	Continuous HDL – measured mg/dL	76	Mean: 39 mg/dL SE: 0.6	16 weeks	NR	NR	% Change from baseline: +7%	
	Arm 3: (M) N-ER 1g +LOV 40mg	Continuous HDL – measured mg/dL	79	Mean: 38 mg/dL SE: 0.6	16 weeks	NR	NR	% Change from baseline: +17%	P<0.05 comparing arms 1 and 3 P<0.05 comparing arms 2 and 3
	Arm 4: (M) N-ER 2g +LOV 40mg	Continuous HDL – measured mg/dL	78	Mean: 39 mg/dL SE: 0.6	16 weeks	NR	NR	% Change from baseline: +32%	P<0.001 comparing arms 1 and 4 P<0.001 comparing arms 2 and 4
Gardner, 1996[57]	Arm 1: (M) LOV 40mg	Continuous HDL – NR mg/dL	14	Mean: 43 mg/dL SD: 11	6 weeks	14	Mean: 44 mg/dL SD: 11	% Change from baseline: +2%	
	Arm 2: (L) N 1.5g +LOV 20mg	Continuous HDL – NR mg/dL	14	Mean: 42 mg/dL SD: 11	6 weeks	14	Mean: 49 mg/dL SD: 18	% Change from baseline: +17%	P=0.04 comparing Arm 1 and Arm 2 at 6 weeks.
Hunninghake, 2003[58]	Arm 1: (M) LOV 40mg	Continuous HDL – measured	61	Mean: 44 mg/dL SE: 1.4	28 weeks	NR	NR	% Change from baseline: +6%	

Author, Year	Arm (Potency)	Outcome Units	Baseline N	Baseline Outcome	Timepoint(s)	N at Timepoint(s)	Outcome at Timepoint(s)	Within Arm Comparisons	Between Arm Comparisons
		mg/dL							
	Arm 2: (L) N-ER 1g +LOV 20mg	Continuous HDL – measured mg/dL	57	Mean: 45 mg/dL SE: 1.5	28 weeks	NR	NR	% Change from baseline: +21%	NR
Insull, 2004[59]	Arm 1: (M) LOV 40mg	Continuous HDL – measured mg/dL	33	Mean: 45 mg/dL SE: 2.0	20 weeks	NR	NR	% Change from baseline: +10% SE: 2.1	
	Arm 2: (L) N-ER 2.5g +LOV 10mg	Continuous HDL – measured mg/dL	34	Mean: 45 mg/dL SE: 2.3	20 weeks	NR	NR	% Change from baseline: +37% SE: 3.6	NR
	Arm 3: (L) N-ER 2.5g +LOV 20mg	Continuous HDL – measured mg/dL	34	Mean: 43 mg/dL SE: 1.7	20 weeks	NR	NR	% Change from baseline: +28% SE: 4.7	NR

HDL high density lipoprotein; IQR interquartile range; N-ER Niacin Extended Release; NR not reported; RSV Rosuvastatin; SMV Simvastatin.

Evidence Table E88. Experiencing any adverse event – niacin

Author, Year	**Arm (Potency)**	**Outcome** **Units**	**Timepoint(s)**	**N at Timepoint(s)**	**Outcome at Timepoint(s)**	**Between Arm Comparisons**
Insull, 2004[59]	Arm 1: (M) LOV 40mg	Count Occurrence of ≥1 AE	20 weeks	33	n: 17 (52%)	
	Arm 2: (L) N-ER 2.5g +LOV 10mg	Count Occurrence of ≥1 AE	20 weeks	34	n: 15 (44%)	NR
	Arm 3: (L) N-ER 2.5g +LOV 20mg	Count Occurrence of ≥1 AE	20 weeks	34	n: 21 (62%)	NR

AE adverse event; IQR interquartile range; LOV Lovastatin; N-ER Niacin Extended Release; NR not reported; RSV Rosuvastatin; SMV Simvastatin.

Evidence Table E89. Withdrawal due to adverse events – niacin

Author, Year	Arm (Potency)	Outcome Units	Timepoint(s)	N at Timepoint(s)	Outcome at Timepoint(s)	Between Arm Comparisons
Hunninghake, 2003[58]	Arm 1: (M) LOV 40mg	Count Withdrawal due to AE	28 weeks	NR	n: (19%)	
	Arm 2: (L) N-ER 1g +LOV 20mg Arm 3: (L) N-ER 2g +LOV 40mg	Count Withdrawal due to AE	28 weeks	NR	n: (10%)	P=0.06 between group differences

AE adverse event; IQR interquartile range; N-ER Niacin Extended Release; NR not reported; SMV Simvastatin.

Evidence Table E90. Elevated AST or ALT – niacin

Author, Year	Arm (Potency)	Outcome Units	Timepoint(s)	N at Timepoint(s)	Outcome at Timepoint(s)	Between Arm Comparisons
Airan-Javia, 2009[55]	Arm 2: (H) SMV 80mg	Count AST and/or ALT consecutive values >3x ULN	12 months	24	n: 1	
	Arm 3: (M) N-ER 2g +SMV 20mg	Count AST and/or ALT consecutive values >3x ULN	12 months	26	n: 0	NR
Bays, 2003[56]	Arm 1: (H) ATV 40mg	Count AST or ALT >3x ULN	16 weeks	NR	n: 0	
	Arm 2: (H) SMV 40mg	Count AST or ALT >3x ULN	16 weeks	NR	n: 0	
	Arm 3: (M) N-ER 1g +LOV 40mg	Count AST or ALT >3x ULN	16 weeks	NR	n: 0	NR
	Arm 4: (M) N-ER 2g +LOV 40mg	Count AST or ALT >3x ULN	16 weeks	NR	n: 0	NR
Hunninghake, 2003[58]	Arm 1: (M) LOV 40mg	Count AST or ALT values >3x ULN	28 weeks	NR	n: 1	
	Arm 2: (L) N-ER 1g +LOV 20mg	Count AST or ALT values >3x ULN	28 weeks	NR	n: 0	NR
Insull, 2004[59]	Arm 1: (M) LOV 40mg	Count AST or ALT values >3x ULN	20 weeks	33	n: 0	
	Arm 2: (L) N-ER 2.5g	Count	20 weeks	34	n: 1 (3%)	NR

Author, Year	Arm (Potency)	Outcome Units	Timepoint(s)	N at Timepoint(s)	Outcome at Timepoint(s)	Between Arm Comparisons
	+LOV 10mg	AST or ALT values >3x ULN				
	Arm 3: (L) N-ER 2.5g +LOV 20mg	Count AST or ALT values >3x ULN	20 weeks	34	n: 1 (3%)	NR

ALT alanine aminotransferase; AST aspartate aminotransferase; IQR interquartile range; N-ER Niacin Extended Release; NR not reported; SMV Simvastatin; ULN upper limit of normal.

Evidence Table E91. Myalgia – niacin

Author, Year	Arm (Potency)	Outcome Units	Timepoint(s)	N at Timepoint(s)	Outcome at Timepoint(s)	Between Arm Comparisons
Airan-Javia, 2009[55]	Arm 2: (H) SMV 80mg	Count Muscle cramps	12 months	24	n: 2	
	Arm 3: (M) N-ER 2g +SMV 20mg	Count Muscle cramps	12 months	26	n: 0	NR
Hunninghake, 2003[58]	Arm 1: (M) LOV 40mg	Count Muscle ache	28 weeks	NR	n: 4 (7%)	
	Arm 2: (L) N-ER 1g +LOV 20mg	Count Muscle ache	28 weeks	NR	n: 2 (4%)	NR

IQR interquartile range; N-ER Niacin Extended Release; NR not reported; SMV Simvastatin.

Evidence Table E92. Elevated creatine phosphokinase – niacin

Author, Year	Arm (Potency)	Outcome Units	Timepoint(s)	N at Timepoint(s)	Outcome at Timepoint(s)	Between Arm Comparisons
Bays, 2003[56]	Arm 1: (H) ATV 40mg	Count CPK >5x ULN	16 weeks	NR	n: 0	
	Arm 2: (H) SMV 40mg	Count CPK >5x ULN	16 weeks	NR	n: 0	
	Arm 3: (M) N-ER 1g +LOV 40mg	Count CPK >5x ULN	16 weeks	NR	n: 0	NR
	Arm 4: (M) N-ER 2g +LOV 40mg	Count CPK >5x ULN	16 weeks	NR	n: 0	NR
Hunninghake, 2003[58]	Arm 1: (M) LOV 40mg	Count CPK >10x ULN	28 weeks	NR	n: 0	
	Arm 2: (L) N-ER 1g +LOV 20mg	Count CPK >10x ULN	28 weeks	NR	n: 0	NR
Insull, 2004[59]	Arm 1: (M) LOV 40mg	Count CPK >3x ULN	20 weeks	33	n: 0	
	Arm 2: (L) N-ER 2.5g +LOV 10mg	Count CPK >3x ULN	20 weeks	34	n: 0	NR
	Arm 3: (L) N-ER 2.5g +LOV 20mg	Count CPK >3x ULN	20 weeks	34	n: 0	NR

CPK creatine phosphokinase; IQR interquartile range; N-ER Niacin Extended Release; NR not reported; SMV Simvastatin; ULN upper limit of normal.

Evidence Table E93. New onset diabetes mellitus – niacin

Author, Year	Arm (Potency)	Outcome Units	Timepoint(s)	N at Timepoint(s)	Outcome at Timepoint(s)	Between Arm Comparisons
Hunninghake, 2003[58]	Arm 1: (M) LOV 40mg	Count Fasting glucose>1.3xULN	28 weeks	NR	n: (7%)	
	Arm 2: (L) N-ER 1g +LOV 20mg Arm 3: (L) N-ER 2g +LOV 40mg	Count Fasting glucose>1.3xULN	28 weeks	NR	n: (4%)	NR
Insull, 2004[59]	Arm 1: (M) LOV 40mg	Count Hyperglycemia	20 weeks	33	n: 0	
	Arm 2: (L) N-ER 2.5g +LOV 10mg	Count Hyperglycemia	20 weeks	34	n: 2 (6%)	NR
	Arm 3: (L) N-ER 2.5g +LOV 20mg	Count Hyperglycemia	20 weeks	34	n: 1 (3%)	NR

DM diabetes mellitus; IQR interquartile range; N-ER Niacin Extended Release; NR not reported; SMV Simvastatin; ULN upper limit of normal.

Evidence Table E94. Treatment adherence – niacin

Author, Year	Arm (Potency)	Outcome Units	Timepoint(s)	N at Timepoint(s)	Outcome at Timepoint(s)	Between Arm Comparisons
Bays, 2003[56]	Arm 1: (H) ATV 40mg	Proportion Compliant with medication	16 weeks	NR	96%	
	Arm 2: (H) SMV 40mg	Proportion Compliant with medication	16 weeks	NR	96%	
	Arm 3: (M) N-ER 1g +LOV 40mg	Proportion Compliant with medication	16 weeks	NR	97%	NR
	Arm 4: (M) N-ER 2g +LOV 40mg	Proportion Compliant with medication	16 weeks	NR	94%	NR
Insull, 2004[59]	Arm 1: (M) LOV 40mg	Count Adherence with medication	20 weeks	33	n: 96%	
	Arm 2: (L) N-ER 2.5g +LOV 10mg Arm 3: (L) N-ER 2.5g +LOV 20mg Arm 4: (M) N-ER 2.5g +LOV 40mg	Count Adherence with medication	20 weeks	100	n: 96%	NR

LOV Lovastatin; N-ER Niacin Extended Release; NR not reported; RSV Rosuvastatin.

Evidence Table E95. Study quality assessment – niacin

Author, Year	2009 CER Jadad Score	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14
Airan-Javia, 2009[55]	NA	U	U	L	L	L	L	N	Y	Y	Y	Y	U	Y	N
Bays, 2003[56]	1	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Gardner, 1996[57]	3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Hunninghake, 2003[58]	4	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Insull, 2004[59]	2	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

CER comparative effectiveness report; H high; L low; N no; NA not applicable; U unclear or unsure.

Q1. What is the risk of selection bias (biased allocation to interventions) due to inadequate generation of a randomized sequence?
Q2. What is the risk of selection bias (biased allocation to interventions) due to inadequate concealment of allocations before assignment?
Q3. For each main outcome or class of outcomes, what is the risk of performance bias due to knowledge of the allocated interventions by participants and personnel during the study (lack of study participant and personnel blinding)?
Q4. Was the care provider blinded to the intervention?
Q5. For each main outcome or class of outcomes, what is the risk of detection bias due to knowledge of the allocated interventions by outcome assessment (lack of outcome assessor blinding)?
Q6. For each main outcome or class of outcomes, what is the risk of attrition bias due to amount, nature, or handling of incomplete outcome data?
Q7. What is the risk of reporting bias due to selective outcome reporting?
Q8. Are there other biases due to problems not covered in 1-6?
Q9. Were all randomized participants analyzed in the group to which they were allocated?
Q10. Were the groups similar at baseline regarding the most important prognostic indicators?
Q11. Were co-interventions avoided or similar?
Q12. Was the compliance acceptable in all groups?
Q13. Was the timing of the outcome assessment similar in all groups?
Q14. Are there other risks of bias?

Reference List

1. Barbi G et al. Effect of Pravastatin and Cholestyramine on Triglycerids-Rich Lipoprotein Particles and Lp(a) in Patients With Type II Hypercholesterolemia. 27. 1992:297-306. PMID:

2. Ismail F, Corder CN, Epstein S, Barbi G, Thomas S. Effects of pravastatin and cholestyramine on circulating levels of parathyroid hormone and vitamin D metabolites. Clin Ther 1990; 12(5):427-30. PMID: 2125243

3. Hunninghake D, Insull W Jr, Toth P, Davidson D, Donovan JM, Burke SK. Coadministration of colesevelam hydrochloride with atorvastatin lowers LDL cholesterol additively. Atherosclerosis 2001; 158(2):407-16. PMID: 11583720

4. Johansson J. Low-dose combination therapy with colestipol and simvastatin in patients with moderate to severe hypercholesterolaemia. 5. 1995:39-44. PMID:

5. Knapp HH, Schrott H, Ma P *et al*. Efficacy and safety of combination simvastatin and colesevelam in patients with primary hypercholesterolemia. Am J Med 2001; 110(5):352-60. PMID: 11286949

6. Comparative efficacy and safety of pravastatin and cholestyramine alone and combined in patients with hypercholesterolemia. Pravastatin Multicenter Study Group II. Arch Intern Med 1993; 153(11):1321-9. PMID: 8507122

7. Schrott HG , Stein EA, Dujovne CA *et al*. Enhanced low-density lipoprotein cholesterol reduction and cost-effectiveness by low-dose colestipol plus lovastatin combination therapy. Am J Cardiol 1995; 75(1):34-9. PMID: 7801861

8. Ahmed S, Ullah E, Ahmed M, Abbas R, Khan MA, Iqbal J. Efficacy of combination of ezetimibe and simvastatin versus atorvastatin in reducing low density lipoprotein-cholesterol in male patients of hypercholesterolemia, at Bahawalpur. Medical Forum Monthly 2008; 19(5):3-9.

9. Araujo DB, Bertolami MC, Ferreira WP *et al*. Pleiotropic effects with equivalent low-density lipoprotein cholesterol reduction: comparative study between simvastatin and simvastatin/ezetimibe coadministration. J Cardiovasc Pharmacol 2010; 55(1):1-5. PMID: 19770669

10. Averna M, Zaninelli A, Le Grazie C, Gensini GF. Ezetimibe/simvastatin 10/20 mg versus simvastatin 40 mg in coronary heart disease patients. J Clin Lipidol 2010; 4(4):272-8. PMID: 21122660

11. Ballantyne CM, Houri J, Notarbartolo A *et al*. Effect of ezetimibe coadministered with atorvastatin in 628 patients with primary hypercholesterolemia: a prospective, randomized, double-blind trial. Circulation 2003; 107(19):2409-15. PMID: 12719279

12. Ballantyne CM, Abate N, Yuan Z, King TR, Palmisano J. Dose-comparison study of the combination of ezetimibe

and simvastatin (Vytorin) versus atorvastatin in patients with hypercholesterolemia: the Vytorin Versus Atorvastatin (VYVA) study. Am Heart J 2005; 149(3):464-73. PMID: 15864235

13. Bardini G, Giorda CB, Pontiroli AE, Le Grazie C, Rotella CM. Ezetimibe + simvastatin versus doubling the dose of simvastatin in high cardiovascular risk diabetics: a multicenter, randomized trial (the LEAD study). Cardiovasc Diabetol 2010; 9:20. PMID: 20492655

14. Barrios V , Amabile N, Paganelli F *et al*. Lipid-altering efficacy of switching from atorvastatin 10 mg/day to ezetimibe/simvastatin 10/20 mg/day compared to doubling the dose of atorvastatin in hypercholesterolaemic patients with atherosclerosis or coronary heart disease. Int J Clin Pract 2005; 59(12):1377-86. PMID: 16351668

15. Catapano AL, Davidson MH, Ballantyne CM *et al*. Lipid-altering efficacy of the ezetimibe/simvastatin single tablet versus rosuvastatin in hypercholesterolemic patients. Curr Med Res Opin 2006; 22(10):2041-53. PMID: 17022864

16. Cho YK, Hur SH, Han CD *et al*. Comparison of Ezetimibe/Simvastatin 10/20 mg Versus Atorvastatin 20 mg in Achieving a Target Low Density Lipoprotein-Cholesterol Goal for Patients With Very High Risk. Korean Circ J 2011; 41 (3):149-53. PMID: 21519514

17. Constance C, Westphal S, Chung N *et al*. Efficacy of ezetimibe/simvastatin 10/20 and 10/40 mg compared with atorvastatin 20 mg in patients with type 2 diabetes mellitus. Diabetes Obes Metab 2007; 9(4):575-84. PMID: 17451425

18. Davidson MH, McGarry T, Bettis R *et al*. Ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia. J Am Coll Cardiol 2002; 40(12):2125-34. PMID: 12505224

19. Feldman T , Koren M, Insull W Jr *et al*. Treatment of high-risk patients with ezetimibe plus simvastatin co-administration versus simvastatin alone to attain National Cholesterol Education Program Adult Treatment Panel III low-density lipoprotein cholesterol goals. Am J Cardiol 2004; 93(12):1481-6. PMID: 15194017

20. Florentin M, Liberopoulos EN, Moutzouri E, Rizos CV, Tselepis AD, Elisaf MS. The effect of simvastatin alone versus simvastatin plus ezetimibe on the concentration of small dense low-density lipoprotein cholesterol in subjects with primary hypercholesterolemia. Curr Med Res Opin 2011; 27(3):685-92. PMID: 21271793

21. Foody JM, Brown WV, Zieve F *et al*. Safety and efficacy of ezetimibe/simvastatin combination versus atorvastatin alone in adults >/=65 years of age with hypercholesterolemia and with or at moderately high/high risk for coronary heart disease (the VYTELD study). Am J Cardiol 2010; 106(9):1255-63. PMID: 21029821

22. Gaudiani LM, Lewin A, Meneghini L *et al*. Efficacy and safety of ezetimibe co-administered with simvastatin in thiazolidinedione-treated type 2 diabetic patients. Diabetes Obes Metab 2005; 7(1):88-97. PMID: 15642080

23. Goldberg AC, Sapre A, Liu J, Capece R, Mitchel YB.

Efficacy and safety of ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia: a randomized, double-blind, placebo-controlled trial. Mayo Clin Proc 2004; 79(5):620-9. PMID: 15132403

24. Goldberg RB, Guyton JR, Mazzone T *et al*. Ezetimibe/simvastatin vs atorvastatin in patients with type 2 diabetes mellitus and hypercholesterolemia: the VYTAL study. Mayo Clin Proc 2006; 81(12):1579-88. PMID: 17165637

25. Tomassini JE, Mazzone T, Goldberg RB *et al*. Effect of ezetimibe/simvastatin compared with atorvastatin on lipoprotein subclasses in patients with type 2 diabetes and hypercholesterolaemia. Diabetes Obes Metab 2009; 11 (9):855-64. PMID: 19508464

26. Guyton JR, Goldberg RB, Mazzone T *et al*. Lipoprotein and apolipoprotein ratios in the VYTAL trial of ezetimibe/simvastatin compared with atorvastatin in type 2 diabetes. J Clin Lipidol 2008; 2(1):19-24. PMID: 21291711

27. Hamdan R, Hajj F, Kadry Z *et al*. Benefit and tolerability of the coadministration of ezetimibe and atorvastatin in acute coronary syndrome patients. J Med Liban 2011; 59(2):65-9. PMID: 21834489

28. Her AY, Kim JY, Kang SM *et al*. Effects of atorvastatin 20 mg, rosuvastatin 10 mg, and atorvastatin/ezetimibe 5 mg/5 mg on lipoproteins and glucose metabolism. J Cardiovasc Pharmacol Ther 2010; 15(2):167-74. PMID: 20147603

29. Kawagoe Y, Hattori Y, Nakano A *et al*. Comparative study between high-dose fluvastatin and low-dose fluvastatin and ezetimibe with regard to the effect on endothelial function in diabetic patients. Endocr J 2011; 58(3):171-5. PMID: 21304215

30. Kerzner B , Corbelli J, Sharp S *et al*. Efficacy and safety of ezetimibe coadministered with lovastatin in primary hypercholesterolemia. Am J Cardiol 2003; 91(4):418-24. PMID: 12586255

31. Lee SH, Kang SM, Park S, Jang Y, Chung N, Choi D. The effects of statin monotherapy and low-dose statin/ezetimibe on lipoprotein-associated phospholipase A(2). Clin Cardiol 2011; 34 (2):108-12. PMID: 21298654

32. Lee SH, Park S, Kang SM, Jang Y, Chung N, Choi D. Effect of atorvastatin monotherapy and low-dose atorvastatin/ezetimibe combination on fasting and postprandial triglycerides in combined hyperlipedemia. J Cardiovasc Pharmacol Ther 2012; 17(1):65-71. PMID: 21386036

33. Lee JH, Kang HJ, Kim HS, Sohn DW, Oh BH, Park YB. Effects of Ezetimibe/Simvastatin 10/20 mg vs. Atorvastatin 20 mg on Apolipoprotein B/Apolipoprotein A1 in Korean Patients with Type 2 Diabetes Mellitus: Results of a Randomized Controlled Trial. Am J Cardiovasc Drugs 2013. PMID: 23728830

34. Liberopoulos EN, Makariou SE, Moutzouri E, Kostapanos MS, Challa A, Elisaf M. Effect of Simvastatin/Ezetimibe 10/10 mg Versus Simvastatin 40 mg on Serum Vitamin D Levels. J Cardiovasc Pharmacol

Ther 2013. PMID: 23288870

35. Matsue Y, Matsumura A, Suzuki M, Hashimoto Y, Yoshida M. Differences in action of atorvastatin and ezetimibe in lowering low-density lipoprotein cholesterol and effect on endothelial function. Circ J 2013; 77(7):1791-8. PMID: 23603824

36. McKenney JM, Jones PH, Bays HE *et al*. Comparative effects on lipid levels of combination therapy with a statin and extended-release niacin or ezetimibe versus a statin alone (the COMPELL study). Atherosclerosis 2007; 192(2):432-7. PMID: 17239888

37. Moutzouri E, Liberopoulos E, Mikhailidis DP *et al*. Comparison of the effects of simvastatin vs. rosuvastatin vs. simvastatin/ezetimibe on parameters of insulin resistance. Int J Clin Pract 2011; 65(11):1141-8. PMID: 21995692

38. Moutzouri E, Tellis CC, Rousouli K *et al*. Effect of simvastatin or its combination with ezetimibe on Toll-like receptor expression and lipopolysaccharide - induced cytokine production in monocytes of hypercholesterolemic patients. Atherosclerosis 2012; 225(2):381-7. PMID: 23062767

39. Okada K, Kimura K, Iwahashi N *et al*. Clinical usefulness of additional treatment with ezetimibe in patients with coronary artery disease on statin therapy. -From the viewpoint of cholesterol metabolism.-. Circ J 2011; 75 (10):2496-504. PMID: 21817821

40. Ostad MA, Eggeling S, Tschentscher P *et al*. Flow-mediated dilation in patients with coronary artery disease is enhanced by high dose atorvastatin compared to combined low dose atorvastatin and ezetimibe: results of the CEZAR study. Atherosclerosis 2009; 205(1):227-32. PMID: 19150064

41. Pesaro AE, Serrano CV Jr, Fernandes JL *et al*. Pleiotropic effects of ezetimibe/simvastatin vs. high dose simvastatin. Int J Cardiol 2012; 158(3):400-4. PMID: 21334753

42. Piorkowski M, Fischer S, Stellbaum C *et al*. Treatment with ezetimibe plus low-dose atorvastatin compared with higher-dose atorvastatin alone: is sufficient cholesterol-lowering enough to inhibit platelets? J Am Coll Cardiol 2007; 49(10):1035-42. PMID: 17349882

43. Robinson JG, Ballantyne CM, Grundy SM *et al*. Lipid-altering efficacy and safety of ezetimibe/simvastatin versus atorvastatin in patients with hypercholesterolemia and the metabolic syndrome (from the VYMET study). Am J Cardiol 2009; 103(12):1694-702. PMID: 19539078

44. Roeters van Lennep HW, Liem AH, Dunselman PH, Dallinga-Thie GM, Zwinderman AH, Jukema JW. The efficacy of statin monotherapy uptitration versus switching to ezetimibe/simvastatin: results of the EASEGO study. Curr Med Res Opin 2008; 24(3):685-94. PMID: 18226326

45. Rudofsky G, Reismann P, Groener JB *et al*. Identical LDL-cholesterol lowering but non-identical effects on NF-kappaB activity: High dose simvastatin vs combination therapy with ezetimibe. Atherosclerosis

2012; 223(1):190-6. PMID: 22633472

46. Stein E, Stender S, Mata P *et al*. Achieving lipoprotein goals in patients at high risk with severe hypercholesterolemia: efficacy and safety of ezetimibe co-administered with atorvastatin. Am Heart J 2004; 148(3):447-55. PMID: 15389231

47. Yamazaki D, Ishida M, Watanabe H *et al*. Comparison of anti-inflammatory effects and high-density lipoprotein cholesterol levels between therapy with quadruple-dose rosuvastatin and rosuvastatin combined with ezetimibe. Lipids Health Dis 2013; 12(1):9. PMID: 23374898

48. Zieve F, Wenger NK, Ben-Yehuda O *et al*. Safety and efficacy of ezetimibe added to atorvastatin versus up titration of atorvastatin to 40 mg in Patients > or = 65 years of age (from the ZETia in the ELDerly. Am J Cardiol 2010; 105(5):656-63. PMID: 20185012

49. Ben-Yehuda O, Wenger NK, Constance C *et al*. The comparative efficacy of ezetimibe added to atorvastatin 10 mg versus uptitration to atorvastatin 40 mg in subgroups of patients aged 65 to 74 years or greater than or equal to 75 years. J Geriatr Cardiol 2011; 8(1):1-11. PMID: 22783278

50. Bays HE, Ose L, Fraser N *et al*. A multicenter, randomized, double-blind, placebo-controlled, factorial design study to evaluate the lipid-altering efficacy and safety profile of the ezetimibe/simvastatin tablet compared with ezetimibe and simvastatin monotherapy in patients with primary hypercholesterolemia. Clin Ther 2004; 26(11):1758-73. PMID: 15639688

51. Athyros VG, Papageorgiou AA, Athyrou VV, Demitriadis DS, Pehlivanidis AN, Kontopoulos AG. Atorvastatin versus four statin-fibrate combinations in patients with familial combined hyperlipidaemia. J Cardiovasc Risk 2002; 9(1):33-9. PMID: 11984215

52. Farnier M, Steinmetz A, Retterstol K, Csaszar A. Fixed-dose combination fenofibrate/pravastatin 160/40 mg versus simvastatin 20 mg monotherapy in adults with type 2 diabetes and mixed hyperlipidemia uncontrolled with simvastatin 20 mg: a double-blind, randomized comparative study. Clin Ther 2011; 33(1):1-12. PMID: 21397769

53. Mohiuddin SM, Pepine CJ, Kelly MT *et al*. Efficacy and safety of ABT-335 (fenofibric acid) in combination with simvastatin in patients with mixed dyslipidemia: a phase 3, randomized, controlled study. Am Heart J 2009; 157(1):195-203. PMID: 19081418

54. Shah HD, Parikh KH, Chag MC *et al*. Beneficial effects of addition of fenofibrate to statin therapy in patients with acute coronary syndrome after percutaneous coronary interventions. World Heart Journal 2008; 1(1):69-77.

55. Airan-Javia SL, Wolf RL, Wolfe ML, Tadesse M, Mohler E, Reilly MP. Atheroprotective lipoprotein effects of a niacin-simvastatin combination compared to low- and high-dose simvastatin monotherapy. Am Heart J 2009; 157(4):687.e1-8. PMID: 19332196

56. Bays HE, McGovern ME. Once-daily niacin extended release/lovastatin combination tablet has more favorable effects on lipoprotein particle size and subclass

distribution than atorvastatin and simvastatin. Prev Cardiol 2003; 6(4):179-88. PMID: 14605511

57. Gardner SF, Schneider EF, Granberry MC, Carter IR. Combination therapy with low-dose lovastatin and niacin is as effective as higher-dose lovastatin. Pharmacotherapy 1996; 16(3):419-23. PMID: 8726600

58. Hunninghake DB, McGovern ME, Koren M *et al*. A dose-ranging study of a new, once-daily, dual-component drug product containing niacin extended-release and lovastatin. Clin Cardiol 2003; 26(3):112-8. PMID: 12685616

59. Insull W Jr, McGovern ME, Schrott H *et al*. Efficacy of extended-release niacin with lovastatin for hypercholesterolemia: assessing all reasonable doses with innovative surface graph analysis. Arch Intern Med 2004; 164(10):1121-7. PMID: 15159270